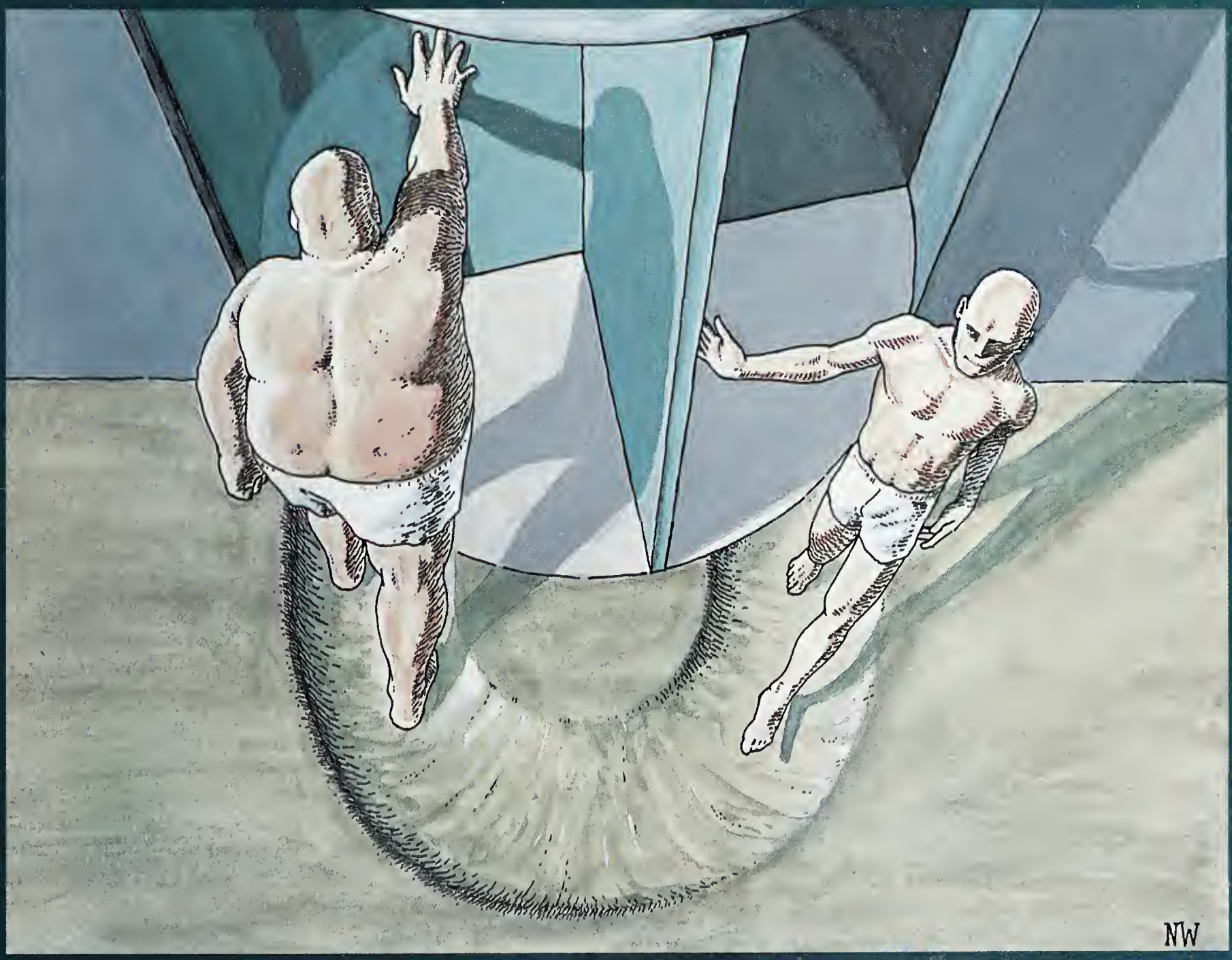
University of Toronto
MEDICAL JOURNAL
Vol. LXVII No. 1



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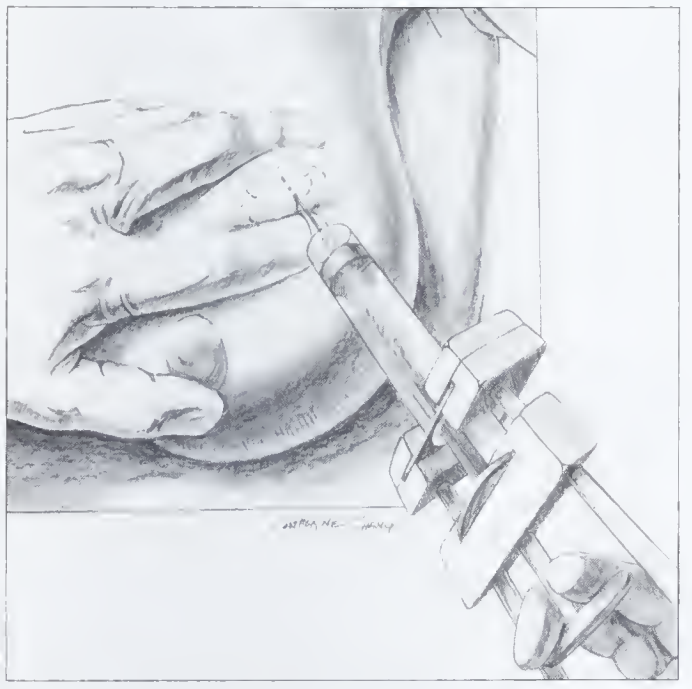

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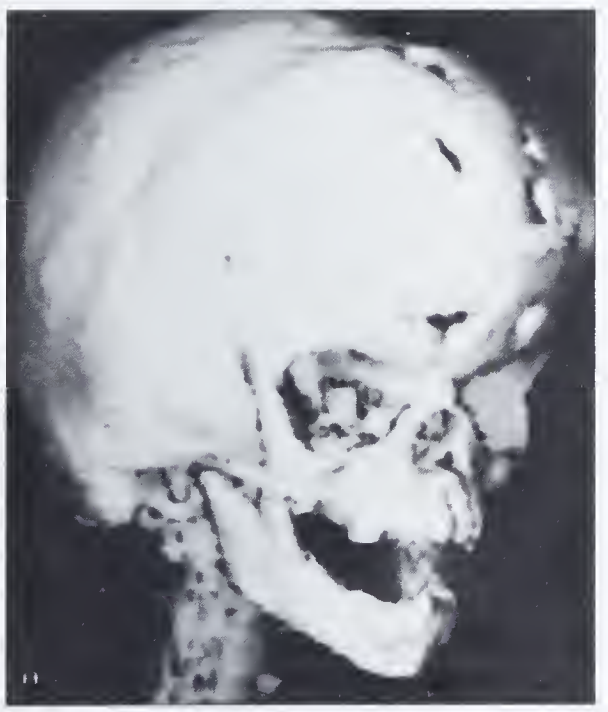

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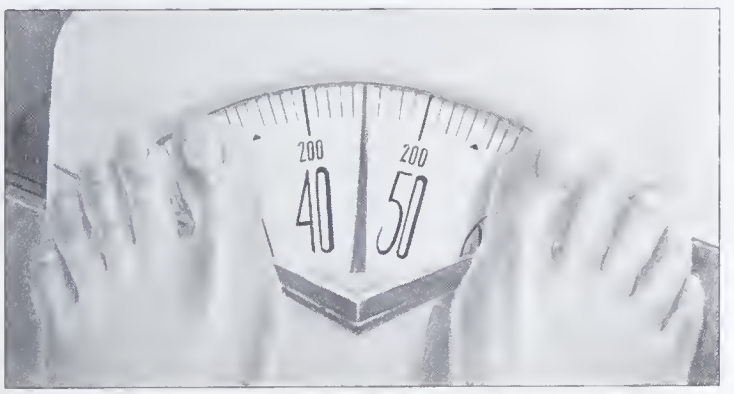

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Editorial

Filiberto Altomare
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This issue marks the 67th year of publication of the *University of Toronto Medical Journal*. This year, we hope to continue to build upon the fine tradition of excellent writing that has established the *Journal* as the premier undergraduate medical journal in this country.

The structure of the *Journal* is similar to last year. We have continued the two new sections begun in the middle of last year, namely 'Quick Dx' and 'Impressions'. We believe that these sections give the *Journal* a broader appeal. For future issues, it is our hope that all abstracts will be published in both English and French allowing the *Journal* to assume a more national flavour.

This year's editors are a select few that have been chosen from many well qualified individuals. We are lucky to have such a broad base of knowledge from which to choose. We are also very fortunate to have Jack Haley as our artistic director. Jack is a well-qualified, talented individual who is completely dedicated to his role. We are very lucky to have him and the other Art as Applied to Medicine students provide us with illustrations for the *Journal*. Superb examples of their work appear in this as well as in all future issues of the *Journal*.

The *Journal* has a variegated readership and thus it is a challenge to produce an issue that will appeal to everyone. We are attempting to do so by publishing a broad range of topics. In this issue, there are excellent articles on the economics of physician pay, the problem of obesity, endocrine hypertension, three dimensional computed tomography, and opportunistic infection. As always the *Journal* remains a platform for student ideas and is therefore a superb opportunity for medical students to gain experience in the publishing world.

Again this year, the *Journal* will award several prizes to articles published. The best article as selected by the editors will receive "The University of Toronto Medical Journal Prize for Literary Excellence" consisting of $100 cash. The two next best articles, again as selected by the editors, will receive $50 each. The department of Orthopaedics will also select the R.I. Harris award from among the submissions in the field. Finally, there is also a prize for the best article in the neurosciences. The winners of all these awards will be published in the third issue of the *Journal*. We hope that these opportunities stimulate students to write for the *Journal*.

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Fine-Needle Aspiration of Breast Lesions: A Review

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Abstract

Cytological diagnosis of breast lesions can be accomplished using fine-needle aspiration. When the technique is performed carefully, adequate cellular material can be obtained for diagnosis of a lesion as benign or malignant. Fine-needle aspiration has excellent potential: the technique is diagnostically accurate, and quick to perform, and results in few complications. New applications utilize immunocytochemical staining techniques on breast aspirates. These stains identify potential tumour-specific prognostic variables. Coupling fine-needle aspiration with immunocytochemistry may augment the clinical use of aspiration techniques.

Introduction

Fine-needle aspiration (FNA) is a technique used for cytological diagnosis of soft tissue masses such as breast tumours. The first large scale series of fine-needle aspirations of breast lesions was reported by Martin and Ellis in 1930.[1] The technique has since been refined[2] and coupled with modern immunocytochemical procedures.[3,4] In light of these advances, the present and prospective clinical roles of FNA of breast lesions might well be re-examined.

Technique

A fine-needle is attached to a syringe and inserted into the breast lesion. Cells are *aspirated* into the needle tip and hub by pulling back on the syringe plunger. The cellular material is *processed* and *cytologically evaluated*.

A. Aspiration

The steps involved in aspirating a breast lesion are shown in Table Ia. In addition, a syringe holder is often helpful since it allows the aspirator to apply controlled amounts of increased suction.

Usually, 21- to 25- gauge needles are used with 10- or 20-mL syringes. Local anaesthetic is not used for three reasons. First, the diameter of needles used for aspiration is similar to that of needles used to inject anaesthetic and therefore, no more painful. Second, local anaesthetics are hypotonic and may lyse aspirated cells. Third, anaesthetic fluid may mask the true location of deep lesions.

Once the needle tip is within the mass, a partial vacuum is created by pulling the plunger back (Fig. 1). The needle is moved back and forth at different angles to sample cells from different parts of the mass. When tissue fluid can be seen in the needle hub, sufficient material for analysis has usually been aspirated. The negative pressure is released before the needle tip is removed from the subcutaneous tissue. This prevents the aspirated material from being sucked into the syringe. To minimize bruising, pressure is then applied to the insertion site.

B. Processing

The needle is removed from the syringe and the syringe is filled with air. The needle is reattached, and the aspirated material is blown from the needle hub onto a cytology slide (Fig. 2). These slides are fixed and stained. A typical protocol for processing the cells for interpretation is described in Table Ib. When performed carefully, an aspiration typically yields between 50 and 200 cells.[5]

C. Cytological Evaluation

The aspirate is usually categorized as one of "malignant", "suspicious for malignancy", "benign", or "insufficient for analysis" by cytopathologists.[6] Acellular aspirates or aspirates lacking morphologically useful information are classed as "insufficient for analysis". Aspirates "suspicious for malignancy" have some atypical cells, but not enough for a positive diagnosis of malignancy.

The major cause of unsatisfactory cytology reports is lack of sufficient interpretable cellular material on the slide. This can occur if the lesion in question is fat or fibrous tissue. However, while defects in processing or interpretation may contribute to this type of result, poor aspiration technique is often the reason for acellular aspirations.[7]

Complications

FNA occasionally produces mild bruising or infection. Pneumothorax is very rare in FNA of breast lesions when the aspiration procedure is carefully performed.[7]

Literature Search

A MEDLINE search of the English language literature between January 1987 and June 1989 revealed fifteen published articles dealing with the accuracy of FNA.[8-22] All dealt with consecutive series of cases, with a minimum of one hundred cases per series. In total, more than 12,000 cases were reviewed. Most investigators grouped the "malignant" and "suspicious for malignant" categories together for analysis.

Statistical parameters of all papers were combined and calculated (Table II). Of note, seven benign cases were

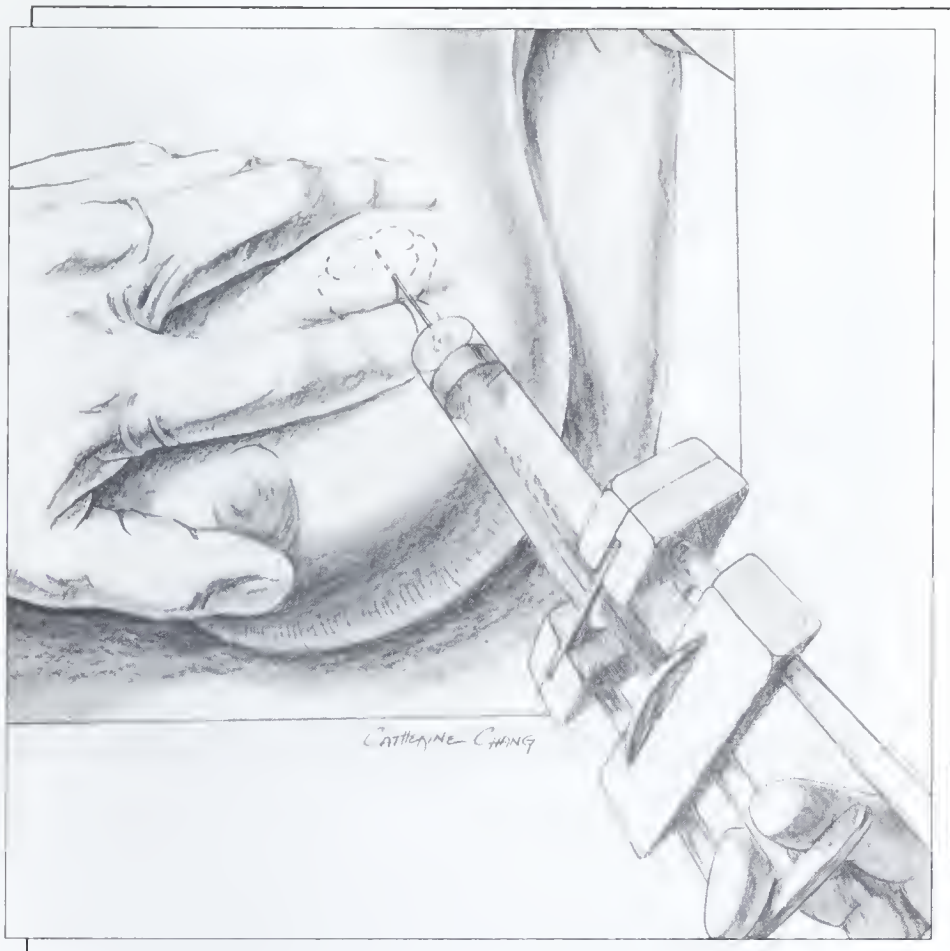

Figure 1: With the needle inside the breast lesion, the plunger is pulled back so that a partial vacuum is created in the syringe.

incorrectly diagnosed by FNA as malignant (false positives). One case was attributed to accidental switching of aspirates;[9] the other six were found to correlate with the pathologists' lack of experience.[9,10,18,22]

The number of samples described as "insufficient for analysis" in a given series, however, was inversely correlated with aspiration experience, that is, the more experienced aspirators produced significantly higher proportions of interpretable aspirates than their inexperienced counterparts.[7]

The articles also addressed the following issues:

1 Physical examination and mammography have become standard diagnostic procedures used for breast lesions. The benefits of the combined use of FNA, mammography, and physical examination were also examined, and FNA was found to significantly improve diagnostic accuracy.[12]

2 FNA also improved the management of patients in whom surgical biopsy was necessary. Patients with malignant lesions discovered by FNA were told of the diagnosis before their surgical biopsies. In general, these patients were better mentally prepared for further surgery and treatment.[17,23]

3 With FNA results known to the surgeons and staff, there was better operating room scheduling and management.[13,23]

In general, FNA was found to be rapid, safe, and cost-effective.[23]

Discussion

Surgical biopsy of breast lesions followed by histological interpretation of stained paraffin sections is presently a very reliable form of diagnosis.[24] However, a day is often required after the biopsy to prepare slides from the paraffin blocks. In comparison, a frozen section diagnosis can usually be given with the patient still under general anaesthetic for the biopsy. But, a small decrease in diagnostic accuracy occurs when a frozen section is used instead of a paraffin-embedded section.[24]

Open biopsies rarely lead to unsatisfactory specimen samples for diagnosis whereas certain types of lesions or an unskilled aspirator can give uninterpretable aspirate results. However, at many hospitals, surgical biopsies for

Table I

A. Aspiration Technique

1 The breast lesion is held between the fingers of the non-dominant hand and against the chest wall.

2 The skin around the proposed insertion site is cleaned with an alcohol swab and allowed to dry.

3 As the dominant hand is holding the plunger of the syringe in the 0-mL position, the needle is inserted into the skin and aimed into the lesion.

4 Once in the lesion, suction is applied by pulling the plunger away from the 0-mL mark.

5 The needle is moved back and forth in the lesion, with the suction still applied.

6 When material appears in the hub of the needle, the suction is released.

7 The needle is withdrawn.

8 Pressure is placed on the site of insertion.

B. Processing Technique

1 The needle is detached from the syringe.

2 The syringe is filled with air.

3 The needle is reattached to the syringe.

4 The contents of the needle are ejected onto a glass slide.

5 The slides are smeared using a coverslip, as in a blood smear.

6 The slides are fixed and stored appropriately.

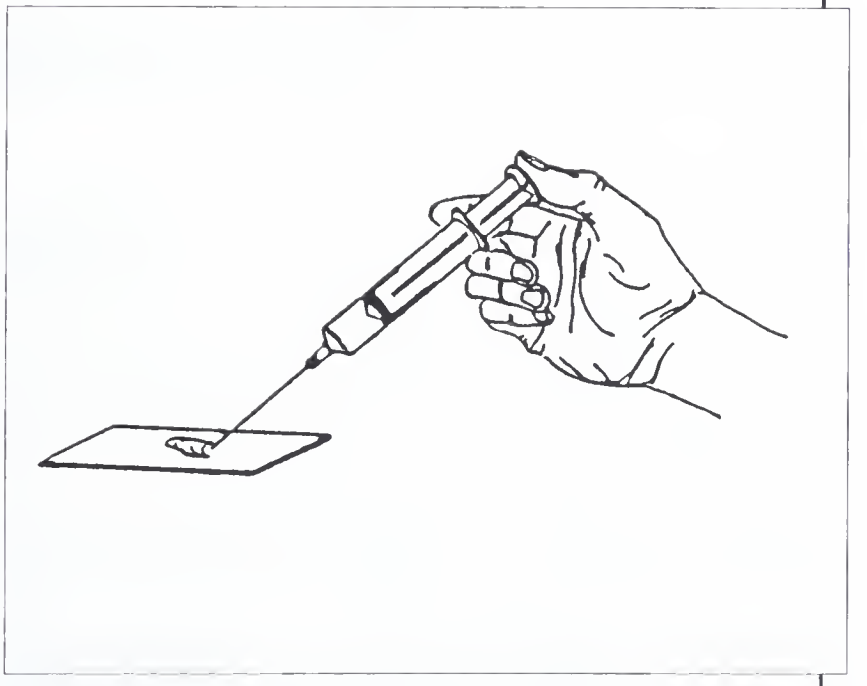

Figure 2: The contents of the needle hub are ejected onto a glass slide for processing and interpretation.

breast lesions often take a week or more to schedule. If a cellular breast aspirate is performed on the initial visit to the surgeon, then a diagnosis can be made within several days. In a few pathology departments, diagnosis within fifteen minutes of aspiration has been tried with some success.[16]

The major use of aspiration cytology presently is as an additional quick, inexpensive diagnostic tool. The statistical strengths of FNA are its high specificity and high positive predictability (see Table II). If the aspirate is diagnosed as malignant, both the surgeon and the patient are prepared in advance for more extensive management of the lesion. In some cases, pre-operative chemotherapy or radiation is given based on FNA diagnosis. On the other hand, any non-malignant FNA report is interpreted with caution since the lesion in question may still be cancerous. Samples "suspicious for malignancy" are usually followed up with an open biopsy. "Benign" diagnoses are a controversial issue since some institutions prefer to wait and re-examine the lesion after several weeks or months.[17] Other centres prefer to do a confirmatory biopsy.[15]

A few medical centres have experimented with replacing the surgical biopsy with FNA of the breast for functional diagnosis of breast lesions, with limited success. Further studies are required before any conclusions can be drawn.[21]

FNA has clearly one advantage over mammography and physical examination: cells from the breast can be quickly and safely obtained. With increasing interest in the immunocytochemical staining of tumour markers (see below), FNA could potentially obtain cells needed for this research.

New Applications

Recently, non-palpable breast lesions (identified through mammography) have been assessed by FNA. The needle is placed within the lesion using stereotactic equipment, and representative cells are aspirated and analysed.[25] Initial reports describing this diagnostic method are promising, but more correlative evidence is necessary to define its role.

Cancer cells obtained by FNA can be characterized with respect to prospective prognostic variables such as DNA content, growth fraction, and the expression of various protein and glycoprotein antigens. For example, the cells obtained from breast cancer aspirates can be analysed by flow cytometry. Using this technology, the DNA content of cells is assessed and displayed in a characteristic histogram, the "DNA profile". Malignant cells containing abnormal amounts of DNA distort this histogram profile, and have been correlated with a poorer prognosis.[26]

The estrogen receptor (ER) content of breast cancer is an important prognostic and management tool. However, the standard biochemical assay for ER requires 0.5 to 1 gram of tissue (10^8–10^9 cells) which can only be reliably obtained by surgical biopsy. In the past year, a number of investigators have used FNA of the breast to characterize ER status through monoclonal antibody assay for the receptor glycoprotein. These immunocytochemical results show high concordance (>90%) with the biochemical assay from surgical biopsy specimens.[27]

Table II Results of Literature Search

Parameter	Range	Median
Sensitivity	75% - 96%	83%
Specificity	90% - 100%	98%
Positive predictability	94% - 99%	97%
Negative predictability	82% - 93%	89%

The above statistics do not include samples *insufficient for analysis.*

Diagnosis	Range	Median
Samples *insufficient for analysis*	10% - 46%	16%
Benign samples	21% - 48%	35%
Samples *suspicious for malignancy*	7% - 30%	15%
Malignant samples	16% - 35%	27%

Two recent developments may increase the quantity of information obtainable from FNA of breast neoplasms. One is the production of monoclonal antibody Ki-67, which detects a nuclear protein expressed by actively dividing cells. By measuring the percentage of cells binding Ki-67, the growth fraction can be determined.[3] Ki-67 binds a nuclear antigen expressed in all phases of the cycle except G0 and the first part of G1. DNA flow cytometry and tritiated thymidine labelling procedures measure only the percentage of cells undergoing the S-phase. Thus, Ki-67 yields a larger growth fraction for the same number of dividing cells and is in this sense, a more sensitive test for cell proliferation.

A second monoclonal antibody has been shown to bind to a 52-kD glycoprotein. Tumour invasiveness appears to be associated with this glycoprotein.[4] Using immunocytochemistry, both Ki-67 and the monoclonal antibody to the 52-kD glycoprotein can be applied to aspirates. Prognostic information from the immunocytochemical markers has yet to be seriously tested. But this type of characterization may become a factor in the future management of breast cancer patients.

Summary

Fine needle aspiration of the breast is an inexpensive, rapid method for obtaining cell samples for diagnostic procedures, while the number of acellular breast aspirates from breast lesions can be reduced with both experience and care. Through characterization of tumour hormone receptor status, ploidy and proliferative rates, FNA has good potential in clinical decision-making.

Acknowledgements

We would like to thank Min Yang Kang for his drawing and Catherine Chang for her illustration.

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Three Dimensional Computed Tomography: Technique and Practical Applications

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Abstract

This paper discusses the theory and applications of three dimensional computed tomographic studies. The principles behind projection of a three dimensional image onto a two dimensional surface are explained. Advantages and disadvantages of this method of diagnostic imaging are discussed. Several examples are shown, comparing normal and abnormal anatomy. These include complex craniofacial deformities, the base of the skull, the vertebral column, the pelvis and joints such as the ankle and knee. The superiority of this technique over conventional radiographic and computerized tomography in these cases is pointed out.

Introduction

In the 1970's computed tomographic scanning (CT scanning) became available for use as a diagnostic tool. Its usefulness in eliminating the overlapping shadows present in conventional radiographs[1] was compromised by its serial-slice nature. The diagnostician had the challenging task of mentally reconstructing the whole image from a series of flat planes.[2] In the last ten years, computer software has been designed to generate three dimensional (3D) pictures using the gray scale to indicate distance from the viewer, as in a black and white photograph.[3] These techniques have been improved to eliminate the original step-like edges ("aliasing artefact")[3] of the early productions giving a smooth, high-resolution, realistic picture. Three dimensional CT scanning can now be used to visualize anatomy from an infinite number of angles after subjecting the patient to only one radiological procedure. Three dimensional scanning has particular value in assessment of several anatomical areas which have been difficult to reveal by conventional radiographic methods.

How CT Scans are Used to Reconstruct a 3D Image

The typical CT study consists of a series of contiguous slices in an axial plane. The closer the slices are, the more accurate the eventual 3D reconstruction will be.[4] In order to construct the 3D picture, the computer represents a 3D volume as a series of small cubic volumes called voxels. Any given voxel will either be part of the object in question or outside it. Voxel surfaces thus represent the surface of the object. Each voxel face can be projected onto a two dimensional (2D) plane perpendicular to the line of sight so that faces at different angles can be represented. Bringing the object to picture form requires that a region of interest be defined and a threshold CT value of x-ray attenuation be selected. This will define a particular CT density that will be represented by the voxel surfaces. The intensity of the face depends on its tilt and its distance from the observer, resulting in a gray scale giving the illusion of depth to the object.[5]

Once the image has been produced, it can be rotated around all three axes to view the reconstruction. Alternatively, a particular area of the anatomy can be isolated by selecting out that part of the scan. This technique is called subregioning and results in an image containing only the information in a discrete area of a particular number of scans in the set. Subregioning is used to disarticulate bones in order to gain an unobstructed view of other surfaces.[4] For example, the mandible can be cut out so that the skull base can be seen clearly, or the top of the skull can be removed to expose the cranial fossae.

Advantages & Disadvantages

The limitations and drawbacks of 3D CT scanning are still noteworthy. Artefacts due to patient movement can be eliminated by sedating the patient prior to scanning. Other artefacts are generated by metallic dental restorations,[5] surgical clips, nasogastric tubes,[4] and plaster casts. Three dimensional scanning is largely limited to bone due to threshold limitations[6] since interfaces must be discernibly different to the computer to be separated. A definite density difference at the junction between different structures is required for effective separation by selection of a threshold of attenuation. Pseudoforamina, which are apparent "holes" in thin bone (for example, orbital roof and cribriform plate), result from partial volume averaging,[7] where a small area of density in a voxel is interpreted as being spread out over the entire voxel. Thus, a thin plate of bone running through a voxel is ultimately represented as a lower density structure totally filling that voxel. Increasing the resolution by decreasing the section thickness will decrease the size of the pseudoforamina[4] and reduce the step pattern at the edges of the image.[7]

Case 1: Head of normal infant of approximately 2 years of age. Note: fontanelle (dark area at apex of head); coronal suture (lateral to fontanelle); metopic suture (in middle of forehead); cupping artefact (horizontal lines at top of skull)

Case 2: Head of Crouzonoid infant of approximately 2 years of age. Note: prematurely fusing fontanelle (at apex of head); prematurely fusing coronal suture (lateral to fontanelle); patent metopic suture (in middle of forehead); depressed bridge of nose (between eyes); hypoplastic maxilla, hyperteloric sockets (eye sockets)

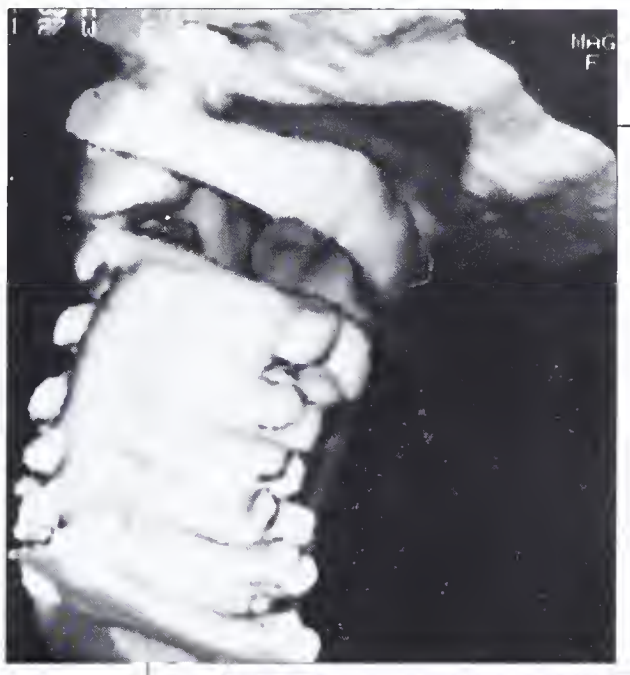
The advantages of this technique offset the additional operator time and cost to the hospital. Three dimensional scanning is used to replace conventional tomograms and exposes the patient to less radiation.[9] As an adjunct to routine radiographic series, this technique is becoming indispensible for craniofacial pre-operative assessment.[9] For example, it can illustrate symmetry, facial clefts, and the extent and pattern of tumour growth. Other advantages include elimination of magnification artefacts and overlapping structures, the ability to make measurements on the image, elimination of communication gaps between the radiologist and the surgeon, and alteration of the image to simulate surgical outcome.[2]

Cases

The following cases illustrate normal anatomy compared to abnormal anatomy and demonstrate the value of 3D reconstruction in visualizing complex anatomy.

Cases 1 & 2

Case 1 shows the skull of a normal infant of approximately two years of age in a frontal oblique projection at 45 degrees to the right. This view shows both sides of the face and can indicate (to some extent) symmetry, profile, and cranial vault shape. The defect at the apex of the skull is the cartilaginous fontanelle; the coronal and metopic sutures are also still patent. The striping at the convexities of the skull is called a cupping artefact.[5] Case 2 is a child of about the same age who was diagnosed with Crouzon's disease. Part of this syndrome includes premature fusion of coronal sutures which results in a shortening of the cranial vault (compare with Case 1). The forehead bulges because it is still capable of growth (note patent sutures) while the rest of the skull is not. Increased intracranial pressure is a frequent complication of Crouzon's disease. Also, this view shows the sunken nasal bridge and the hypoplastic maxilla.



Case 3: Postero-inferior view of the base of the skull. Note: C1 - first ring of bone below skull; C2 - bifid spinous process (1st spinous process)

Case 4: Postero-inferior view of the base of a skull with absence of the posterior arch of C1. Note: C2 - 1st bifid spinous process; space normally occupied by arch of C1 (above C2)

Cases 3 & 4

Case 3 is a posteroinferior view of the base of the skull showing the bifid spinous process of the axis and the articulation of the atlas with the occipital condyles. Case 4 is the same region showing absence of the posterior arch of C1. This region is difficult to visualize with conventional methods since structures overlap when projected in two dimensions.

Case 5: Posterior view of spinal column – lower thoracic vertebrae. Note: body of vertebra (large mass at bottom of picture); vertebral canal (slightly dark area above body); articulation with rib (far lateral of picture - where vertebra overlaps rib); rib (white bars exiting picture laterally)

Case 6: Posterior view of spinal column in cervical region with fracture of posterior arch of C2. Note: spinous process of C2 (2nd vertebra from top); fracture (dark area lateral to spinous process of C2)

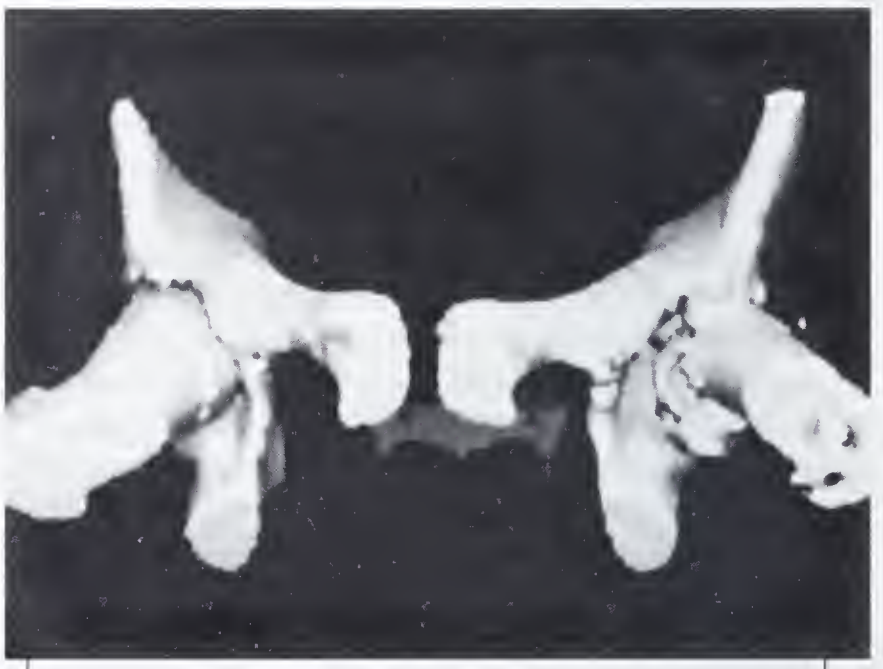
Cases 5 & 6

These cases show posterior views of the vertebral column. Subregioning techniques have allowed projection of just a few vertebrae, sliced to allow a view into the vertebral canal. Gaps are interpreted as disc spaces. The normal image (Case 5) shows lower thoracic vertebrae, and the articulations of the ribs are visible laterally. Case 6 shows cervical vertebrae demonstrating a fracture of the posterior arch of C2. The spine can also be subregioned vertically in hemisection to assess defects in the vertebral canal, vertebral foramina, and vertebral bodies. The angle of surgical approach can be simulated by rotating the image; this coupled with a clear view of lesions causing changes in contour allows a great deal of pre-operative planning.

Case 7: Anteroinferior view of normal pelvis of child. Note: pubis (most medial corner of bone - anterior); ischium (most inferior corner of bone); iliac crest (most superolateral crest of bone); bladder (light mass in centre of picture behind pubis); head of femur (long bones - lateral of picture)

Cases 7 & 8

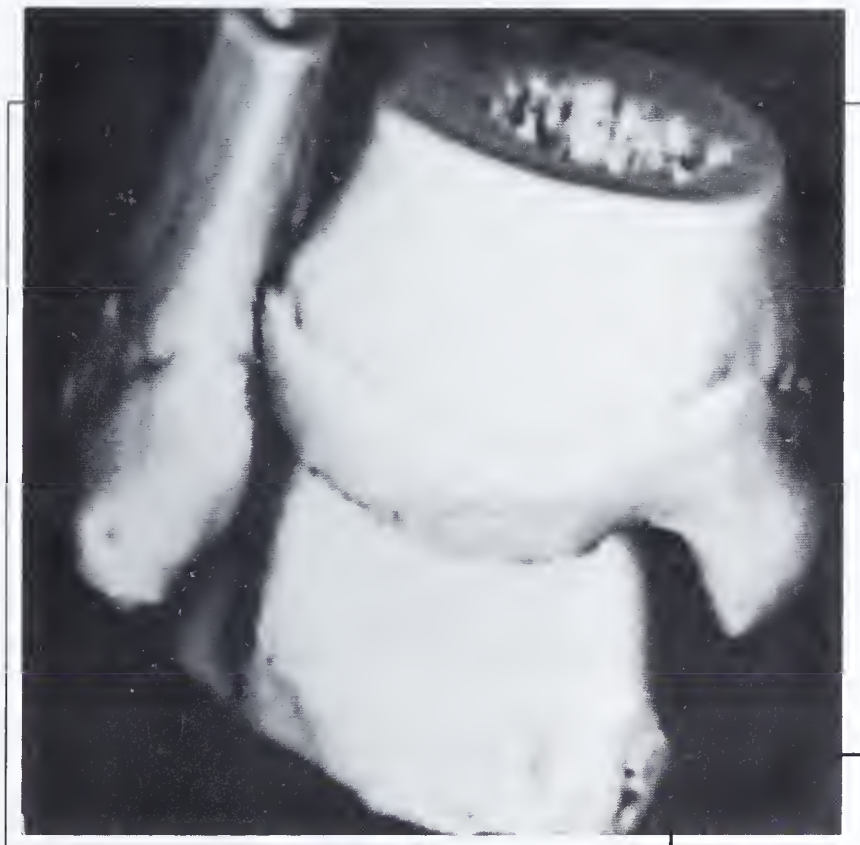
Case 7 shows a normal pelvis of a child which has been subregioned to isolate the pelvic girdle. The sutures between the pelvic bones are as yet unfused in this young child. The bladder can be seen behind the pubis, with the bladder neck protruding just below the inferior ramus of the right pubic bone. Case 8 is a frontal inferior view of a young teenager's pelvis which has been sliced at a higher level than Case 7 so that the ischium is not seen. This view shows an epiphyseal plate fracture and avascular necrosis of the left femoral head. This angle of view of the pelvis cannot be obtained with conventional radiographs.



Case 8: Anteroinferior view of teenaged child's pelvis showing epiphyseal plate fracture & avacascular necrosis of left femoral head. Note: sectioned pubis (white masses medial of picture); sectioned ischium (light masses lateral to pubis & medial to femurs); epiphyseal plate fracture (left femur - near oscoxae); avascular necrosis of head of femur (head of left femur inferior to epiphyseal plate)

Cases 9 & 10

Case 9 is an anterosuperior projection of the normal right ankle of a child. The unfused epiphyseal plates can be seen in both fibula and tibia. Three dimensional CT scans reconstruct complex joints such as the ankle and the knee so realistically that the images look like photographs of skeletons. Case 10 shows two views of a fractured left ankle. The fracture line extends along the epiphyseal plate at the lateral aspect of the distal end of the tibia, and spirals upwards along the posterolateral aspect of the tibial shaft. The white cylindrical artefact at the edges of the picture are parts of the plaster cast included in the scan.



Case 9: Anterosuperior view of child's normal right ankle. Note: fibula (narrow bone at left); tibia (large bone at right); talus (most inferior bone)

Case 10B: Posterior view of left ankle showing spiralling fracture line in tibia. Note: fibula (at left of picture - narrow bone); tibia (large bone at right); fracture line (dark line spiralling up tibia)

Case 10A: Anterior view of left ankle showing fracture along epiphyseal plate of tibia. Note: tibia (large bone in centre of picture); displaced fragment (inferior & right of tibia); fracture line (between fragment & tibia); cast artefact (white masses at top corners of picture)

Conclusions

Three-dimensional CT scanning is a valuable adjunct to conventional radiographic series and planar CT series for the assessment of certain disorders. Current endeavours include development of computer processing to reduce artefacts in surface reconstruction images,[8] attempts to process Magnetic Resonance Imaging data, and improvements in soft-tissue boundary recognition.[6] These techniques should help eliminate some of the difficulties in assessment of diagnostic images, and improve patient care.

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Obesity: The Problem and Management

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Abstract

Obesity is the most prevalent malnutrition problem in Western society, and appears to have a multifactorial etiology. It is associated with serious health complications. Although many forms of treatment exist, their success in reducing weight permanently has been poor. Efforts should be placed on education in the awareness and prevention of obesity, with the hope that future generations will be able to control this disorder.

Introduction

Obesity is the most common form of malnutrition in North America. Obesity has often been viewed as being a direct result of gluttony; however, this concept is an oversimplification. Indeed, obesity is the result of a positive energy balance, but the reasons for this are many.[1] In Canada and U.S.A., as well as France and Germany, it is estimated that one-third of the population is overweight, with an associated decrease in life expectancy.[2] The prevalence of obesity in the general population is increasing, as is obesity among infants and children. Obesity which originates in childhood is later associated with the poorest treatment prognosis. This paper reviews proposed etiologies and treatments for obesity, as well as the significant complications of the disease.

Criteria for Diagnosis of Obesity

The following are the four most commonly used criteria:

1 An **accumulation of fat** due to storage of excess energy as adipose tissue. As an indication of the problem, 3500 extra Calories will produce 1 lb of fat weight gain. Hence, 100 extra Calories (eg. one cookie) per day for one year will result in a 10 lb weight gain.[3] As well, a distinction must be made between "overweight" and "obesity": overweight means the body weight is in excess of some arbitrary standard and, therefore, can apply to an athlete with increased muscle mass; obesity means an excess of adipose tissue.

2 **20% or greater above "ideal" body weight** as indicated by the *1983 Metropolitan Life Insurance Height and Weight Tables* (Table I).[4] These tables are based on the 1979

Table I

THE METROPOLITAN HEIGHT AND WEIGHT TABLES
Height Weight (in lbs)

MEN			
Feet Inches	*Small Frame*	*Medium Frame*	*Large Frame*
5 2	128-134	131-141	138-150
5 3	130-136	133-143	140-153
5 4	132-138	135-145	142-156
5 5	134-140	137-148	144-160
5 6	136-142	139-151	146-164
5 7	138-145	142-154	149-168
5 8	140-148	145-157	152-172
5 9	142-151	148-160	155-176
5 10	144-154	151-163	158-180
5 11	146-157	154-166	161-184
6 0	149-160	157-170	164-188
6 1	152-164	160-174	168-192
6 2	155-168	164-178	172-197
6 3	158-172	167-182	176-202
6 4	162-176	171-187	181-207

WOMEN			
Feet Inches	*Small Frame*	*Medium Frame*	*Large Frame*
4 10	102-111	109-121	118-131
4 11	103-113	111-123	120-134
5 0	104-115	113-126	122-137
5 1	106-118	115-129	125-140
5 2	108-121	118-132	128-143
5 3	111-124	121-135	131-147
5 4	114-127	124-138	134-151
5 5	117-130	127-141	137-155
5 6	120-133	130-144	140-159
5 7	123-136	133-147	143-163
5 8	126-139	136-150	146-167
5 9	129-142	139-153	149-170
5 10	132-145	142-156	152-173
5 11	135-148	145-159	155-176
6 0	138-151	148-162	158-179

Weights at ages 25-59 based on lowest mortality, wearing shoes with 1 inch heels and indoor clothing (3 lb for women, 5 lb for men). Prepared by the Metropolitan Life Insurance Company. The tables have also been converted to kilograms.[4]

Build Study, where mortality statistics were received from 25 life insurance companies in the U.S.A. and Canada, involving an 18-year follow-up of 4.2 million insured individuals. This "ideal" or desirable weight is the weight which was found to be associated with maximum life expectancy, and interestingly, is less than the average weight in society. The weights are given in a range for body frame (small, medium, and large) based on caliper elbow-breadth measurements,[4] with the middle 50% of elbow-breadth arbitrarily falling into the medium frame group.

There are a number of criticisms of these tables: 1) the population consisted of a disproportionately large number of Caucasians; 2) the insured population is in a higher economic group than the general population; 3) weights were self-reported in 10% of clients; 4) weights were taken with individuals wearing clothes and shoes with 1 inch heels for both males and females; 5) applicants with major diseases (heart disease, cancer, or diabetes) at the time of insurance policy issuance were excluded; 6) clients ranged from ages 25-59, but the weight associated with the lowest mortality actually increased slightly with age. Nevertheless, these tables are still the best available estimate of ideal body weight. Ideal weight may be calculated by a simple formula (Fig. 1) which gives values that correspond to the midpoint of the ranges given in Table I for the medium frame.[5]

3 The **Pinch Test** involves measuring skinfold thickness over the triceps in the midarm location (most commonly used), or below the scapulae, or on the lower chest wall, abdomen, suprailiac area, and thighs. A midarm subcutaneous fat-fold of >2.54 cm, measured with calipers, indicates obesity.[6]

4 **Body Mass Index (BMI)** or **Quetelet Index** is the most useful measure of weight status for the healthy adult population aged 20-65. It is calculated as weight (kg) divided by height (m) squared, and accurately compares fatness for all heights.[7,8] A BMI of 23 indicates normality, ≥30 indicates obesity and ≥47 indicates morbid obesity. An abnormally high or low (<20) BMI is associated with decreased longevity.

Etiology

For an individual patient, identification of as many contributing factors as possible may be helpful in devising a treatment strategy. In general, more women are overweight than men of equal age. This may be related to the higher percentage of fat that women have in their bodies (25%), as compared to men (15%).[9] There are many factors involved in the etiology of obesity:

1 **Endocrine:** Primary endocrine diseases associated with obesity are uncommon, and none give rise to massive

ADULT FEMALE: 5 FEET = 119 LB; FOR EACH ADDITIONAL INCH, ADD 3 LB.
ADULT MALE: 5 FEET 3 INCHES = 135 LB; FOR EACH ADDITIONAL INCH, ADD 3 LB.

Divide by 2.2 to change to kg.

Formula for calculation of ideal weight, which corresponds to midpoint of range for medium frame of the *Metropolitan Tables*, with a margin of error of less than 1%. Decreasing or increasing the result by 10% allows for small or large frame, as determined by elbow-breadth.[4,5]

Figure 1: Calculation of Ideal Weight

obesity. Examples include hypercortisolism, insulinoma, hypogonadism, polycystic ovary syndrome, and hypothalamic syndromes.

2 Socioeconomic and Educational Status: For both males and females, those with some post-secondary school education are less likely to be obese than those with lower levels of education. In affluent societies, both children and adults of lower economic status are more likely to be obese. As income rises, men tend to be more obese (possibly due to sedentary occupations) while women are thinner.

3 Energy Balance: This involves an energy (caloric) intake which is greater than energy expended (law of thermodynamics). With increasing weight gain in the adult, adipocytes hypertrophy until the individual reaches approximately 170% of ideal weight. With a further increase in weight there is hyperplasia of adipocytes, which remains throughout life.[9] Obesity in infancy and childhood is associated with hyperplasia of adipocytes and is therefore more difficult to reverse.

4 Genetics: Human obesity is under strong genetic control. If one parent is obese, 40% of offspring are obese. If both parents are obese, 80% of offspring are obese, as compared to 7% if both parents are of normal weight. Studies of twins (raised together and separately) found that genetic factors override environmental experiences in predicting the development of obesity. As well, studies of adopted children showed their weight to be related to their biological rather than their foster parents.[10]

5 Basal Metabolic Rate (BMR): The obese may biochemically expend less energy than the lean by possessing a lower BMR. However, the BMR of obese individuals has been found to be variable.[11]

6 Set-Point Theory: Individuals appear to be programmed for a particular weight. During over-feeding of normally lean individuals, metabolic rate and heat production increased, burning off energy as though to maintain a biologically set weight. When some of these same individuals became fat, they required more calories to maintain the excess weight than the usually obese.[12] This may explain why most obese dieters have difficulty in weight reduction, as their body, acting as if starved, struggles to defend its weight by conserving energy.

7 Brown Adipose Tissue (BAT): BAT, located in cervical, axillary, perirenal, periadrenal, para-aortic, and intercostal regions, is profusely vascularized. Its stimulation by norepinephrine from sympathetic nervous system innervation results in non-shivering thermogenesis.[13] Cold exposure and hyperphagia are stimulators of BAT. In animals, diet-induced BAT thermogenesis (different from the thermic effect of food itself) plays an important role in buffering changes in food intake, decreasing when intake is low and increasing in response to hyperphagia. If this buffering is impaired, then overall energy expenditure decreases and obesity results.

8 Psychological Phenomena: Some individuals turn to food for depression, anxiety and boredom, leading to obesity. In others, obesity may be part of a personality disorder. As well, distorted eating cues as an infant (getting food for inappropriate reasons, such as when the baby cries because of being wet or lack of attention) may lead to persisting obesity if appropriate eating habits are not learned by adulthood.

9 Pregnancy: Normally, females gain approximately 12 kg during pregnancy due to breast and uterine hypertrophy, the fetus, placenta and amniotic fluid. Body fat deposition makes up 4 kg of this weight gain (of value during breast-feeding since extra energy is needed for milk production). Many women lose this weight postpartum, but in some, the onset of obesity coincides with pregnancy, with increased adipose accumulation with successive pregnancies.

Food intake also increases in the postovulatory phase of the menstrual cycle, via menstrual cycle induced appetite. These regular intervals of increased intake may contribute to obesity in many women.[9]

Complications of Obesity

Obesity is associated with serious sequelae affecting major organ systems, including cardiovascular, pulmonary, gastrointestinal, genitourinary, and musculoskeletal (Table II). The massively obese have problems with basic activities of normal life. They cannot find clothes in their size, fit into a chair with arms, buckle a seat-belt, pass through turn-stiles, cross their legs, put on their shoes, cut their toenails, keep themselves clean, or engage in sexual activity. Massively obese men (>170% of ideal weight) aged 25-35 have a mortality-rate 12 times that of their normal weight contemporaries.[14]

Body fat distribution is significant. When men become heavier, fat tends to accumulate around the trunk, also known as "above waist", upper body, android, or "apple" distribution. When females gain weight, fat tends to increase all over the body, but particularly on the thighs and buttocks, also known as "below waist", lower body, gynoid, or "pear" distribution. These fat distribution patterns are quantitated using the "waist-hip ratio", which is the ratio of waist (abdomen) girth divided by hip (gluteal) girth, both in centimeters. Values >1 for males and >0.8 for females are associated with increasing health risks.[8] This corresponds to the android fat distribution, which is associated with an increased incidence of hypertension, atherosclerosis, and diabetes.[15] This fat distribution appears to be a sex hormone epiphenomenon, since females with the android distribution have higher plasma levels of testosterone, while males with the gynoid distribution show increased levels of estrogens (via androgen to estrogen conversion in adipose tissue).[16]

Conservative Intervention

1 Fad Diets: These result in initial rapid weight loss due to water and sodium loss. Consequently, these quick cures for obesity should be avoided. Examples include the grapefruit, Zen Macrobiotic, rotation, and Herbal Life diets. This group also includes acupuncture and hypnosis.

2 **Total Fasting:** This is a dangerous way to lose weight and requires comprehensive medical surveillance; 70% of weight lost is the result of water and protein loss.

3 **Very Low Calorie Diets** or **Protein Sparing Fasts (PFS):** These generally include diets of less than 800 kcal/day. The PSF is the most effective non-surgical treatment of obesity, designed to produce rapid weight loss while preserving lean body mass. Protein intake alone permits lipolysis, with attendant ketosis with consequent anorexia, although the latter relationship has not been proven. The PSF was introduced in the 1970's and consists of 300-400 kcal/day along with 1.5-2.0 L of water. This provides 1-1.5 g (2-2.5 g for children) of high biological value protein/kg of ideal weight/day, supplemented by multivitamins with minerals.[17,18] Nitrogen balance is achieved in about 6 weeks.

Table II

COMPLICATIONS OF MASSIVE OBESITY

Cardiovascular Risk Factors
- Hypertension
- Hyperlipidemias
- Decreased plasma high density lipoproteins
- Non-insulin-dependent diabetes

Pulmonary
- Dyspnea and fatigue
- Alveolar hypoventilation and somnolence (Pickwickian syndrome)
- Obstructive sleep apnea
- Pulmonary Embolism

Gastrointestinal
- Fatty liver
- Cholelithiasis
- Hiatus hernia and reflux
- Carcinoma of colon in males

Reproductive and Genitourinary
- Irregular menses, amenorrhea, and infertility*
- Urinary stress incontinence in women
- Endometrial hyperplasia and carcinoma of endometrium*
- Carcinoma of breast*
- Pre-eclampsia and caesarean sections
- Hypothalamic hypogonadism in males
- Carcinoma of prostate

Other Medical Complications
- Debilitating degenerative arthritis of weight-bearing joints and low back
- Varicose veins
- Venous stasis ulcers
- Deep vein thrombosis
- Foul intertrigos, boils, and rubbing inner thighs
- Hernias
- Immobility
- Accident proneness

Psychosocial
- Discrimination (job, education, socially)
- Social withdrawal
- Loss of self-esteem and depression

* Obesity is associated with a decrease in sex-hormone-binding-globulin, resulting in an increase in free circulating androgens; moreover, androgens undergo aromatization to estrogens in adipose tissue, which increases circulating estrogen levels.[11]

These diets should be distinguished from some unbalanced commercial very low calorie liquid-protein diets which were associated with sudden deaths, presumably due to cardiac arrhythmias from a deficiency of certain essential amino acids.[19] Medical surveillance is mandatory as there can be several adverse side-effects (Table III).

4 **Low Calorie Balanced Diets:** These generally provide 800-1200 kcal/day, using a wide variety of table foods. Within these energy ranges and with appropriate food choices, the required daily nutrient intake can be met. Some of these diets can be monotonous, and they are not successful in the markedly obese. The diet energy content must be individualized and the patient must have realistic weight loss expectations of 0.5-1.0 kg/wk, in keeping with the fact that it took years to put on the weight.

5 **Low and High Carbohydrate Unbalanced Diets:** The low carbohydrate diet has high satiety value because of its high protein and fat content. The low carbohydrate consumption-induced ketosis is responsible for a rapid initial weight loss due to diuresis. The low carbohydrate diets have inadequate fibre content, and the high fat content with attendant cholesterol overload would impose an additional atherogenic risk, particularly on the coronary arteries.

High carbohydrate diets induce weight loss through limited food choices, and tend to be nutritionally unbalanced in terms of protein, vitamins and minerals. Diarrhea, muscle wasting and hair loss are frequent side-effects.

6 **Behavioural and Psychological Therapy:** This method uses the following five components: 1) a pre-treatment psychosocial assessment; 2) self-monitoring or record-keeping (i.e. a daily food and eating pattern diary); 3) control of antecedent conditions surrounding eating, eg. sitting in the family room or turning on the TV as a cue to snack; 4) institution of a sensible approach to permitting intake of special occasion foods; 5) positive self-coping mechanisms.[20] This method has not been successful with the massively obese. Psychological and psychiatric therapy may be necessary in patients where obesity is linked to such underlying problems as depression, stress, and binge-eating.

7 **Exercise:** Exercise must suit the patient's overall health and age. It raises the BMR (which has often been lowered in a dieter whose body is trying to conserve energy) and keeps it raised for hours after vigorous activity. Other effects include a reduction in blood pressure and plasma glucose and plasma fat levels, along with muscle build-up (at the expense of fat), and induction of a feeling of well-being. Exercise does not always increase, and in fact, may decrease appetite (a good thing). More fat and less lean tissue are lost with adjuvant diet restriction than with a diet alone.[9]

8 **Support System:** Family, friends, and physician can yield support and reassurance, helping the obese patient cope with and maintain the uphill struggle. Self-help groups and weight loss clinics, such as Weight Watchers and TOPS, can be helpful.

9 **Drugs:** Various drugs have been tried in obese pa-

Table III

COMMON SIDE-EFFECTS OF VERY LOW CALORIE DIETS OR PSF'S

- Dizziness
- Fatigue
- Cold Intolerance
- Dry Skin
- Hair Loss
- Amenorrhea
- Liver Damage
- Kidney Impairment
- Dehydration
- Potassium Loss (Arrhythmias)
- Protein Loss
- Depression
- Orthostatic Hypotension

tients, but none have been demonstrated to be effective in producing significant, maintained weight loss. Some of the more studied drugs are presented below:

a) Anorectic drugs, particularly amphetamines, can be taken (in the morning) on a short-term basis to provide initial help in dieting, by centrally suppressing appetite and peripherally dissipating heat. Most anorectic drugs are modifications of the phenyl ring and side-chain of d-amphetamine. Side-effects include CNS stimulation (causing anxiety and insomnia), sympathetic nervous system stimulation (causing tachycardia and a raised B.P.), and toxic psychosis (rare). Abuse potential is present, as is severe depression following cessation of the drug.

Fenfluramine, one of the d-amphetamine analogues, interferes with brain serotonin metabolism (where serotonin inhibits food intake) and actually causes drowsiness instead of CNS stimulation.

b) Bulk fillers like methylcellulose increase the bulk in the stomach, thereby reducing hunger.

c) Thyroid hormone is effective only in very high doses and leads to thyrotoxicosis-like symptoms.

d) Human Chorionic Gonadotropin injections to reduce truncal obesity have not proven effective.

10 Intragastric Balloons: The balloon's intent was to produce satiety by filling the stomach. However, the stomach dilates to compensate, requiring further balloon inflations. These balloons, which ultimately break, may cause small bowel obstruction or pass uneventfully per rectum.

Surgical Intervention

Surgery is used only as a last resort in patients >100 lb (45 kg) above ideal weight or twice ideal weight (termed *morbid obesity* because of resultant serious, progressive, debilitating diseases). Candidates must have failed to sustain adequate weight loss on extensive conservative regimens (where a 10 kg weight loss is not adequate for these patients). The surgical candidate must understand the risks and potential sequelae of the surgery, be cooperative, and agree to lifelong follow-up.

Operations have been performed to cause either energy malabsorption or energy intake restriction. Jejunoileal bypass operations were abandoned because of electrolyte abnormalities, possible liver deterioration, renal calcium-oxalate stone formation, arthralgias, bloating and flatus. Gastric restrictive operations (eg. vertical banded gastroplasty or Roux-en-Y gastric bypass) restrict the stomach's capacity and thus the amount of food a person is capable of eating at one sitting. Overindulgence will result in discomfort, nausea and vomiting. The gastric bypass has the added feature of inhibiting intake of sugary liquids which would cause "dumping" syndrome when they would empty into the jejunum. These operations along with medical and nutritional follow-up offer selected morbidly obese patients the greatest likelihood of substantial, maintained weight loss of any therapy presently available.

Recidivism

The relapse rate among obese individuals is substantial, with only 2-5% of those who underwent a supervised weight regimen maintaining the weight loss permanently.[21] Reasons for this dismal success rate (besides the aforementioned genetic and set-point aspects) may include unreal expectations, monotonous meal plans, and the concept of dieting itself, as it implies a temporary effort (i.e., "on", then "off"). Former eating habits may be resumed following dieting, and patients often binge on foods which had been forbidden while dieting. To counter this, decreased intake rather than abstinence from certain foods should be employed. Lastly, the "yo-yo" pattern (i.e. repeated weight loss followed by weight regain) may put back more fat, since with each successive cycle, metabolic changes make the post-dieting weight regained higher in fat than muscle.[22] Concomitantly, repeated dieting may cause loss of self-esteem, a sense of failure, and depression.

Prevention

It is thus clear that there is no universally effective treatment for obesity. Primary prevention focuses on decreasing the incidence of obesity, and includes measures to decrease over-feeding in infancy and sedentary lifestyle by education programs. Secondary prevention aims at reducing the prevalence of obesity by early identification of obesity and improved treatment, involving, for example, periodic weighing of infants to identify obesity early. Future prospects include demonstration of genetic determinants of obesity to allow understanding and development of programs of prevention.

Acknowledgement

The authors are indebted to Dr. Daniel A.K. Roncari, Chief of Medicine at Sunnybrook Medical Centre and Professor of Medicine, for review and suggestions.

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A Microeconomic Analysis of Remuneration Systems & the Impact They Have on Physician Behaviour

Sherif P. Nessim B.A.Sc. M.B.A. M.D. 8T9

Abstract

Three methods of physician remuneration (fee-for-service, capitation, and salary) were examined by microeconomic analysis in order to illustrate how physician behaviour changes based on the method of remuneration used.

Microeconomic analysis is best suited for this work, as it allows one to graphically illustrate the impact of different remuneration schemes on the demand for medical services. It was assumed that the physician's goal was to maximize utility function (degree of satisfaction) by increasing net income and leisure time. Of the three remuneration schemes, only fee-for-service provided physicians with financial incentives capable of generating an appropriate level of medical care per patient. In contrast, both capitation and salaried incomes induced physicians to provide what they believed to be adequate medical care per patient.

The impact of each remuneration scheme as a financial burden on the health care system was also evaluated. In Canada we live in a socialistic society which offers health care to the public at a basically fixed rate, regardless of the number of services rendered. Doctors can manipulate the demand for their services so as to reach a target income while at the same time straining the reserves of the system. Extra billing may produce a more efficient system where patients would not seek unnecessary help as often, physicians would tend to induce less demand, and medical health care would save money.

Introduction

Traditionally, physicians have been paid for their services using one of the following systems: **A** fee-for-service, **B** capitation, or **C** salary. The fee-for-service system is like piece-work in industry, where the physician is paid a fee for each unit of service, be it an office call, hospital visit, surgical operation, etc. The capitation system, in contrast, uses the patient number, rather than the medical act, as the unit of remuneration. Thus, a physician receives a predetermined amount of money for each patient serviced, regardless of the number of medical acts performed per patient. The salary method pays the doctor for the time spent, regardless of the number of units of service provided or the number of patients whose health is supervised. Salaries may be full-time or part-time, and the latter may be defined in terms of a specific number of hours or days of work, or they may involve a "medical session" of variable length. The amount of the salary is usually varied in accordance with the doctor's professional qualifications, experience, level of responsibility, etc.

This paper reviews these three methods of paying physicians and assesses how they influence the physician's effort to maximize the utility function. This is important, as the method used to pay the physician has tremendous implications on the reserves of the medical financial system. Likewise, it heavily influences the quality of health care rendered to patients. What is to the advantage of the health care system is to the disadvantage of the patients, however, as we live in a society where the system is run by elected officials who must seek favour with those who readily use the health care system.

Economic Analysis

The health care market is a market with Supplier-Induced-Demand (S-I-D) and information asymmetry. Thus, physicians are accused of increasing their incomes by capitalizing on their patients' uncertainties[1] and lack of medical knowledge. This shifts the demand for medical services,[2,3] which, in turn, allows physicians to schedule more appointments for patients than are actually needed. Gabel and Redisch[4] described the fee-for-service practitioner as a profit entrepreneur who acts as an agent for the patient, providing information that will influence the patient's future purchases of medical care. The physician's conflict of interest arises from the fact that the agent also provides a part of the medical services.

In order to assess physician behaviour, one must begin to consider his objectives. Most can be grouped under one of seven headings: **1** income, **2** leisure, **3** ethical medical practice, **4** community services, **5** charity, **6** intellectual and research motives, and **7** dislike for supervision.[5] Only the

Key words:
- Utility Function
- Utility
- Supplier-Induced-Demand
- Information Asymmetry
- Marginal Cost
- Marginal Revenue
- Moral Hazard

All these terms are defined in the glossary.

first three objectives were considered in this economic analysis. Thus, in assessing the physician's behaviour, the following statement can be applied: doctor's utility = U (net income, work, ethics), where a doctor's utility increases as the net income and moral behaviour (ethical behaviour) increases, but declines with an increased work load. The degree of satisfaction (U) will vary from one doctor to another and the utility obtained from ethical behaviour will range from 0 to some finite amount.

Fee for Service

Figure 1a illustrates the use of fee-for-service for medical remuneration. P1 is the price being paid to the physician for the service rendered; DD is the demand curve for the market in question. The demand curve intersects the marginal revenue line of the physician at a higher point than it does the physician's marginal cost line. Thus, increasing the number of physician services will increase the net income even more than is expected. The end result is that the physician will induce demand for medical services, so as to shift the DD line to $D^{I}D^{I}$. At this level, the physician makes the same money per service rendered, yet the net income increases as more patients (i.e., M1 as opposed to M0) are seen. The income has been increased by the amount defined as P1M1–P1M0.

At this point, the marginal benefit is still greater than the marginal cost and, financially, it is feasible to further shift the demand curve by inducing more patients to come for services. Once demand shifts to $D^{II}D^{II}$, income has been maximized, and marginal cost will be greater than marginal benefits for any additional service rendered. Hence, each additional unit of work rendered will produce a greater cost than it does income to the physician, and even a doctor with minimal ethics will not further induce demand. The greatest profit to the doctor will be realized at an income of P1M2.

There are, however, factors which limit the extent to which doctors will no longer induce demand. For example, most doctors receive utility out of acting ethically. Acting unethically, via inducing demand and shifting the demand curve to the right, increases their marginal cost. This causes a left shift in the marginal cost curve. The greater the disutility from the unethical behaviour, the greater the left shift of the marginal cost curve, as seen in **Figure 1b**. As a result, the ethical physician shifts demand, but only up to a point. The maximum demand will be shifted to $D^{III}D^{III}$, as going beyond this will yield a lower profit picture. The end result for an ethical physician is that demand will be shifted far less than for the unethical doctor. Thus, the ethical doctor's income will be less than that of the unethical doctor by an amount defined as P1M2–P1M3. This difference in income is equal to the peace of mind which the ethical doctor has received by not cheating the patients.

Figure 1c depicts an opposite scenario. Here a doctor puts so much emphasis on maintaining an ethical behaviour that no demand beyond what is approriate is induced. The income is now defined as P1M0 and the income not

Figure 1: Case scenarios depicting physician behaviour with Fee For Service Renumeration

Legend (refer to text for description)
D: Demand Schedule
MC: Marginal Cost
MR: Marginal Revenue
P: Price per medical service rendered

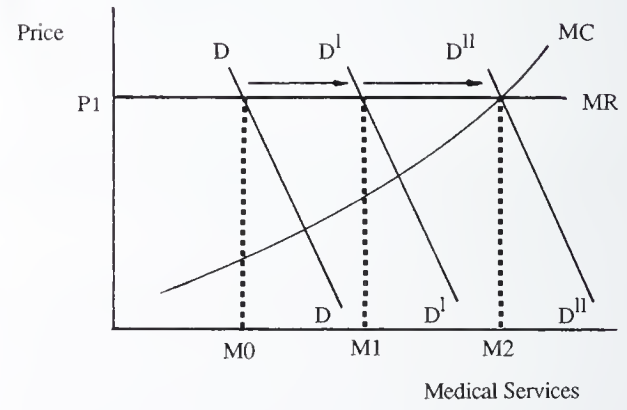
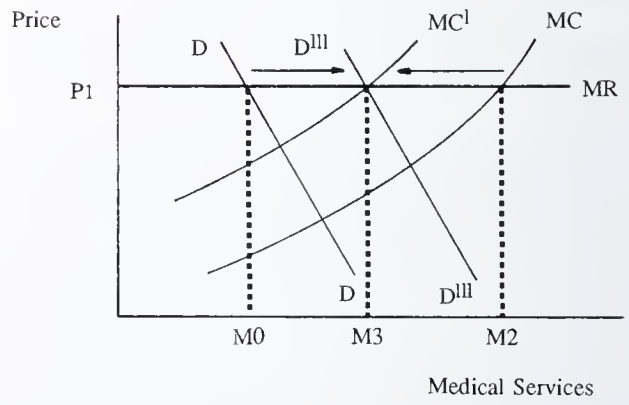


Figure 1(a)



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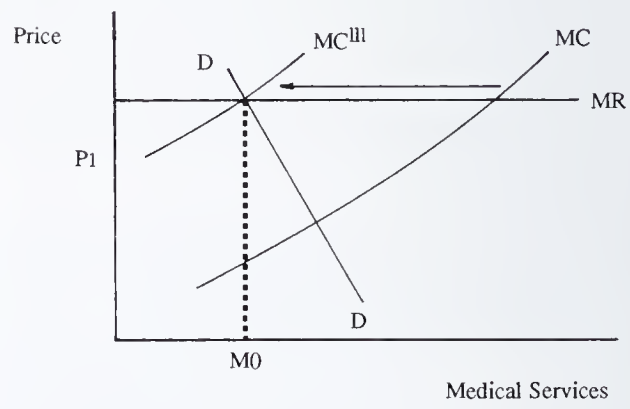


Figure 1(c)

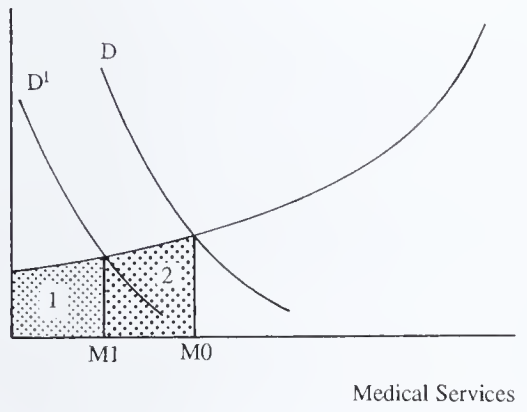
realized is P1M2–P1M0. Nonetheless, for the same reason as in **Figure 1b**, the physician is satisfied.

Another factor that limits the S-I-D behaviour of the physician is that utility is obtained from leisure time. The more demand is shifted, the less leisure time the physician will have.

Thus, the three most important factors to be considered in assessing the behaviour of the fee-for-service physician are income, leisure, and ethics. Each will influence the doctor's desire to induce demand and the weighting each doctor gives to these factors will vary. The weighting given to income must be, at the very least, some finite number greater than zero. Based on the doctor's desires, the weighting given to the remaining two variables can vary from zero to some finite number. This will depend on the doctor's ethics and desire to have leisure time balanced against income.

Figure 2: Analysis of the Price vs. Medical Services curve obtained from Capitation.

Legend (refer to text for description)
Mc: Marginal Cost



Capitation Scheme

In the capitation scheme a given physician will be allocated a fixed patient number with a predetermined income for a given time period. The only variable that alters the physician's net income is the cost of providing services, as S-I-D generates a zero marginal revenue. Therefore, under capitation, the physician's utility is defined as: Maximize U (costs, leisure time, ethics). A physician will maximize utility function by lowering costs and increasing leisure time. The ethics variable will once again range from 0 to some finite value, and vary from one doctor to the next. This remuneration system is depicted in **Figure 2**, where the original demand curve is DD. The cost of caring for M0 patients is given by the area under the marginal cost curve, and is equal to *Area 1 + Area 2*. To increase the net profit, the physician will try to decrease the number of times a patient visits the office, thus shifting the demand schedule to the left at D^1D^1. In this case, M1 patients are seen at a cost determined by the area under the MC curve equal to Area 1 (which is smaller than the previous area). By decreasing the total number of patients, the physician increases leisure time, which further works to increase the utility. Again, a limiting factor will be the moral conduct of the physician. The lower the moral conduct, the further the shift to the left, while, in the extreme case of full ethics, there will be no shift at all. There is, however, a minimum amount of health care that must be given to the patient regardless of how low the moral standards of the doctor are (i.e. to avoid a malpractice suit), so that there is a limit to how much the demand schedule can be shifted to the left.

Salary

With the salary method of medical remuneration, as in capitation, the income is fixed. However, for the salaried physician there are no costs, assuming an institution covers the expenses and the salary of the physician. Utility is then defined as: Maximize U (leisure time, ethical behaviour). The doctor attempts to maximize the time devoted to research, leisurely activities, and/or acquiring peace of mind (as dictated by ethics) by lowering as far as is ethically comfortable the number of visits from patients. If the physician has no ethics at all, then the number of patient visits will be few. This satisfies the institution for which the physician works, since it lowers its costs, assuming it is an institution working on an allocated budget. Conversely, the ethical doctor will not try to shift demand as much to the left but will try to give patients the best medical care they require. Thus, a physician with a fixed income will never produce too much care. Instead of using time to provide more than the "appropriate" amount of care, time would be devoted to leisure and research, leading to an increase in utility.[3]

The Effect of Health Insurance

Feldstein[6] has shown that health insurance leads to increased societal costs, termed welfare loss, due to "moral hazard".[7] By definition, a moral hazard is a situation which enables an insured patient to see a physician more often than an uninsured patient, thus allowing the doctor to induce demand upon desire at no additional cost to the patient.

User Fees

To curb the welfare losses and deal with moral hazard, one solution may be a system based on user fees, where patients are charged for each visit to the doctor. This would serve to place part of the burden of the cost onto the patient, as shown in **Figure 3a**.

Due to the present structure of the OHIP schedule (i.e. with no extra billing), the price per service to the patient is 0. Based on the demand schedule, the quantity of services ordered would be S0, and as described earlier, this results in moral hazard. User fees (Pu) would reduce the number of patient visits and the number of services rendered to S1, thus reducing the doctor's income from P1S0 to P1S1. This would likely result in a shifting by the doctors of the demand curve to the right, as described by Evans,[8] and

Figure 3: Case scenarios illustrating the influence of extra-billing and user fees.

Legend (refer to text for description)
P1: Price per medical service rendered
Peb: Extra-billing fee per service rendered
Pu: User fee payable per service rendered
S0: Quantity of service rendered with no extra charge imposed
S1: Quantity of service rendered if a user fee imposed
S2: Quantity of service rendered if extra-billing imposed

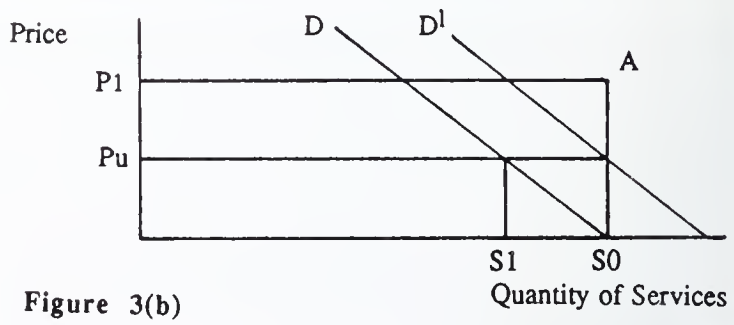


Figure 3(b)

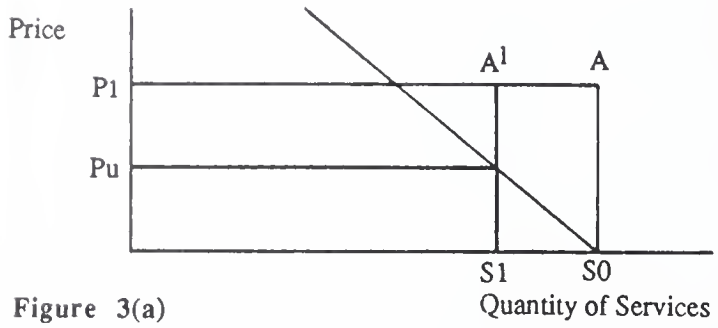


Figure 3(a)

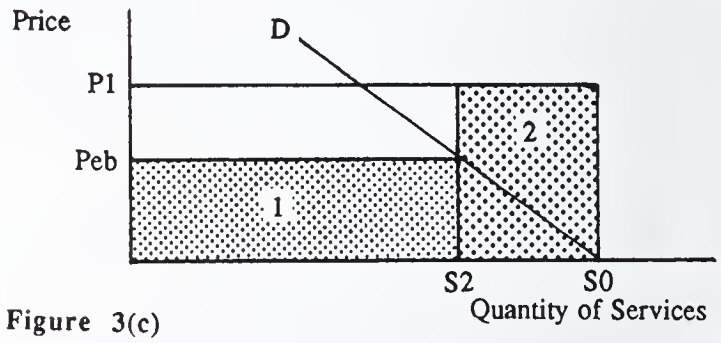


Figure 3(c)

shown in **Figure 3b**. With the shifted demand curve and Pu, the quantity of services is again at S0 and physicians recapture the income they would have lost. The government's attempt to lower needless patient visits would not have worked. However, it would have at least generated an income for itself equal to PuS0, which helps to offset medical costs. A more efficiently run system would allow the doctors to extra bill. In so doing, it would still place part of the burden on the patient to help counteract moral hazard, while at the same time it would remove the incentive for doctors to shift demand, as outlined below.

With extra billing, the number of patient visits would drop, similar to the user fee concept, and patients would be more discriminant about their need to see the physician. Since the number of visits would drop, the amount paid to doctors from the government would also drop. However, unlike the case of user fees, the doctors would not try to induce demand since the income would not change as payments go to the doctor and not to the government. It is assumed that the demand generated is such that the total income received from the government and the patient is the same as it was before extra billing when the number of patient visits was S0. As shown in **Figure 3c**, the income generated by the doctor was P1S0 – all from the government. Physicians should be equally happy with S2 services rendered if they can extra bill at Peb, as this would yield them the same income as long as: $P1S0 - P1S2 = PebS2$ (*Area 1 = Area 2*). (A lack of such an equality under the extra billing scenario would result in only a modest shift in demand so that the physician could still reach this target income). If Area 1 equals Area 2, a greater net profit occurs since physicians' costs at S2 are less than at S0 (fewer services rendered) and leisure time will have increased. Both these situations will increase the doctors' utility function.

Conclusions

This discussion illustrates how physicians can shift demand for their services in order to reach a target income goal. The patient would not likely resist such a shift in demand so long as he/she is not burdened with any part of the financial cost. This arrangement will yield the greatest amount of health care, but it is a tremendous financial strain on the health care system. Cost to the system can be controlled through either capitation or salaries but these may result in health care which is less than optimal. These systems also dissatisfy the physicians for it not only makes them employees of the government, but it also limits their income.

The fee-for-service system can be used and still contain the costs of medical care. With extra billing, the physicians would be satisfied having not sacrificed income, and the financial strain on the system would be less. In theory, the patient should be happier also because now he/she is part of a more efficiently-run system with less S-I-D. If time is more valuable than the extra billing charges, the patient should be happy too, due to fewer office visits.

However, in general, patients are not happy paying more than they have to, and it is irrelevant to the patient that the whole system becomes more efficient. What concerns patients most is the cost, as they would prefer to pay nothing. The government reverts to the less efficiently run system of fee-for-service without extra billing and user fees. This is, in part, a result of the pressures to remain in power by capturing the majority of votes from those who enjoy the current health care system.

Glossary

Utility Function: the variables that an individual uses in determining his satisfaction, i.e. net income, amount of leisure, etc.

Utility: satisfaction.
Supplier-Induced-Demand (S-I-D): a situation whereby a supplier of a service is in control of the demand for that service.
Information Asymmetry: knowledge shared by the supplier and recipient of a service is not equal. This leads to S-I-D., i.e. the patient has no medical knowledge and thus relies on what the doctor prescribes for him.
Marginal Cost: increase in cost for each additional unit of service offered.
Marginal Revenue: increase in revenue for each additional unit of service offered.

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Opportunistic Infection in Non-immunocompromised Patients: Three case reports of fatal CNS involvement by rare infectious agents

Paul J. Marchetti 9T0, and Douglas Kondziolka M.D.

Abstract

Multiple cerebral abscesses due to *Haemophilus aphrophilus* occurred in a 59 year old man with no history of immunosuppression. A 43 year old man suffered cerebral nocardiosis with lower spine involvement as the primary symptomatic site. As in the first case, there was no suspicion of immunocompromise. Finally, a 53 year old woman with a history of rheumatic heart disease acquired an especially rare bacterial endocarditis. The agent is a *Moraxella*-like organism, classified as CDC group M6. Despite standard therapies, each of the cases were fatal, and the enigma of opportunistic infections in nonimmunocompromised patients remains. Several suggestions are presented to reconsider opportunism and immunocompromise.

Case 1

A fifty-nine year old right-handed railroad conductor, on returning home from work one day, was noted to be excessively drowsy. He progressed to an unarousable state. His gait was ataxic, being unable to stand without assistance. One episode of vomiting was reported. On admission, he was hypothermic (34°C) with an elevated white blood cell count. Chest radiograph showed two right upper lobe lesions. CT revealed multiple enhancing cerebral lesions. He was started on dexamethasone 6 mg I.V. q8h and then transferred to St. Michael's Hospital.

Other than a past history of depression, gout, hypertension and alcohol intake, the patient was shown to be previously well. Medications on admission included imipramine, allopurinol, and nadolol. He was a non-smoker.

On admission, his examination revealed a temperature of 37.8°C and a blood pressure of 140/70 mm Hg. There was moderate neck stiffness. His chest exam showed good air entry with no adventitious sounds. There was a Grade II/VI systolic ejection murmur. No organomegaly was found in the abdomen. Rectal examination was normal. Neurologically, his eyes opened spontaneously and he scored 10 out of 15 on the Glasgow coma scale. He did not speak or follow commands but moved all extremities well. He localized with his upper extremities and withdrew his lower extremities. His pupils were 4 mm and reactive with bilateral downward deviation of the eyes. No papilledema was visualized. He had spastic lower limbs with a right upgoing toe. Lab work on admission showed Na 133 mmol, K 4.0 mmol, Cl 96 mmol and pCO2 27 mm Hg. Hematology revealed normal PT and PTT, borderline anemia and a leukocytosis of 28.5 x 10^9/L.

The patient was intubated and ventilated and underwent percutaneous fluoroscopic lung biopsy of the right upper lobe mass. Post-biopsy he developed a pneumothorax and required chest tube insertion. Intraoperatively, a right frontal burr hole was made for brain biopsy as well as ventriculostomy. Penicillin G was started after a quick section showed polymorphs and necrotic brain. Despite antibiotic therapy he progressed into deeper coma. Bacteriology found a Gram-negative bacillus, initially identified as *Eikenella*, later found in fact to be *Haemophilus aphrophilus*. Within three days of admission, the patient's neurological status continued to deteriorate with an increase in intracranial pressure and the patient died.

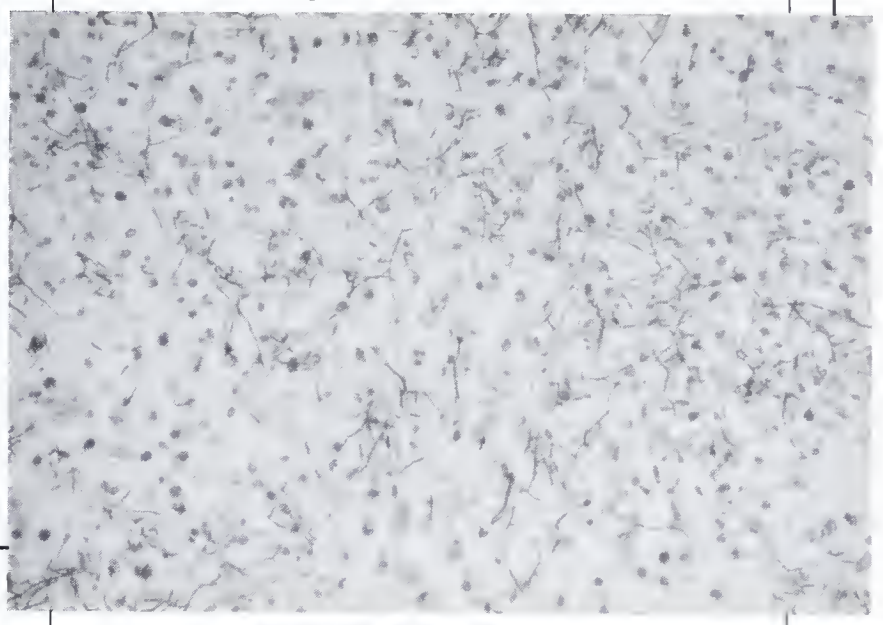
Examination of the brain at autopsy showed tonsillar herniation and multiple bilateral cerebral and cerebellar thin-walled abscesses, averaging one centimetre in diameter (Fig. 1). Culture from these abscesses, as well as from the lungs, grew *Haemophilus aphrophilus*. The lungs showed evidence of confluent bronchopneumonia and abscesses, three centimetres in diameter, were found within the substance of the right upper lobe. Microscopic examination of this tissue showed old granuloma formation which stained negative for mycobacteria. Similar granulomata were also found in the mediastinal lymph nodes, suggesting the possibility of a Gohn complex (the initial focus of primary pulmonary tuberculosis). Examination of the heart revealed no evidence of endocarditis or valvular disease. The liver was mildly enlarged and showed fibrosis and siderosis consistent with chronic alcohol abuse. The spleen was also mildly enlarged and congested with evidence of siderosis. Mild nephrosclerosis was seen in the kidneys.

Case 2

A forty-three year old male car painter developed new onset of lower back pain, unresponsive to nonsteroidal anti-inflammatory agents. Within four weeks, numbness and weakness developed in the left leg. After a further two weeks, the patient presented with a five-day history of

Figure 1: Case 1 – Cerebral section shows multiple bilateral thin-walled abscesses.

Figure 2: Case 2 – Gram stain of bone marrow examined under high power shows significant concentration of *Nocardia*.



progressive confusion and drowsiness. A CT scan was taken which showed multiple intracranial enhancing mass lesions. He was subsequently transferred to the neurosurgical service.

There was a history of hypertension, alcohol consumption and smoking. Two years prior, he had been treated for a lung lesion for which no diagnosis was identified but had responded to penicillin.

Physical exam revealed a drowsy middle-age man with facial telangiectasia, a fever of 39°C and marked meningismus. There were no palpable lymph nodes, and pulmonary and cardiac auscultation were unremarkable. Abdominal exam showed some left lower quadrant tenderness and a firm liver edge palpable 2 cm below the costal margin. Neurologically, he was drowsy and confused but was arousable to voice and would obey commands. His external ocular movements were full and no nystagmus was seen. There was no other cranial nerve deficit. At motor testing there was some mild weakness of the left leg, but it was difficult to assess due to poor cooperation. Sensation appeared to be intact to pin prick. Reflexes were normal except for absent knee jerks and Babinski responses were equivocal. Lumbar spine plain films showed no evidence of abnormality. CT scan of the brain showed enhancing mass lesions in the cerebellar hemispheres as well as along the ventricular surface of the lateral ventricles. Lab work showed a hyponatremia (Na = 130 mM) and hematology revealed a borderline anemia and mild leukocytosis. The clinical diagnosis was one of bacteremia leading to meningitis and possible brain abscess or metastatic brain tumor.

A tissue diagnosis was urgently sought and the patient was taken to the operating room for a left occipital craniotomy and incision and drainage of a left cerebellar abscess. A left occipital ventricular drain was inserted. A gram stain showed Gram positive fungi suggesting a diagnosis of actinomycetes. Penicillin was used at a dose of 4 000 000 units q6h. On Day 3, his mental status deteriorated such that he was inappropriately mumbling and not following commands. His intracranial pressure reading was 15 cm H_2O. The organism identified from the cerebellar biopsy

Figure 3: Case 2 – Section of midbrain shows purulent meningitis.

was *Nocardia* and he was treated with trimethoprim-sulfamethazole (TMP-SMX) and penicillin. Because of progressive obtundation, the patient was re-intubated for ventilation control. However, he continued to deteriorate neurologically secondary to increased intracranial pressure which rose to 20 cm H_2O. On Day 4, his blood pressure dropped to approximately 50/30 mm Hg with an intracranial pressure of 26 cm H_2O. Fluids were used to maintain the blood pressure between 90 and 100 mm Hg systolic. A central venous pressure reading showed 14.5 cm H_2O. His pupils became fixed and dilated with no corneal response and no response to pain. Neurological dysfunction continued and the patient was pronounced dead on Day 6.

At autopsy, findings of lumbar spine osteomyelitis (Fig. 2), cerebral and cerebellar abscesses, acute purulent meningitis (Fig. 3), renal and pulmonary abscesses indicated the

extent of nocardiosis. Cranial examination also showed vasculitis in the subarachnoid space at the base of the brain with vessel wall destruction and compromise of the lumen. Ventriculitis was extensive from the lateral to the fourth ventricles with accompanying evidence of mild hydrocephalus. Examination of the lungs revealed foci of bronchopneumonia and punctate abscesses bilaterally, shown microscopically to be positive for *Nocardia*. Abdominal examination showed mild hepatomegaly with microscopic evidence of portal triaditis and some bridging fibrosis, but no "true" cirrhosis was identified. The spleen was similarly enlarged, soft and apparently congested. The heart showed no evidence of endocarditis or valvulopathy. Microscopically, there was no evidence of epicardial inflammation.

Case 3

A fifty-three year old female presented with "flu-like" symptoms, fever, and back and leg pain. A past history of rheumatic heart disease and the presence of a heart murmur on physical examination prompted treatment at a local health centre. Blood culture disclosed Gram-negative bacilli and she was treated with broad spectrum antibiotics. Her course was precipitous. She became hypotensive and oliguric, requiring intensive care monitoring for fluid management. She progressed onto renal failure as well as pulmonary edema, necessitating intubation and ventilation. Fourteen days after presentation she progressed onto coma and was transferred to St. Michael's Hospital, where a CT scan of the brain showed massive right frontal lobe hemorrhage with mid-line shift and intraventricular extension (Fig. 4). Following craniotomy and evacuation of the hematoma, she experienced problems with intracranial pressure and continued to deteriorate. She died fifteen days after the initial presentation.

Autopsy revealed evidence of acute bacterial endocarditis superimposed on chronic rheumatic disease of the mitral valve. Examination of the valve tissue showed inflammation and the presence of a Gram-negative coccobacillus confirmed to be CDC (Centre for Disease Control) group M6. The aortic valve showed mild thickening and minimal stenosis of the outlet. Evidence of splenic infarction was accompanied by the visualization of a nearby arteriolar mycotic aneurysm. Both kidneys showed evidence of acute proliferative glomerulonephritis and acute tubular necrosis. Hemorrhagic necrosis within the right frontal lobe was visualized with extension into the ventricular system causing subfalcial and uncal herniation. No source for the hemorrhage could be demonstrated at autopsy.

Discussion

Case 1: *Haemophilus aphrophilus* septicemia

Since the first description of *Haemophilus aphrophilus* in a fatal case of endocarditis in 1940,[1] approximately 133 cases of infection due to *Haemophilus aphrophilus* have been reported. The most comprehensive work was carried out by Bieger et al.[2] in a review of 42 patients over a 12 year period at the Mayo Clinic. Only 2 of 42 isolates were from brain abscesses. Total reported brain abscesses due to *Haemophilus aphrophilus* now number 21, this patient included.[2,3] In 8 of these, congenital heart disease was found. However, in an equal number of cases, no associated condition was found.[2,3] Interestingly, endocarditis due to *Haemophilus aphrophilus* has not been reported with neurological complications,[2] although such complications occurred in 39% of the cases of bacterial endocarditis reviewed by Pruitt et al.[4] *Haemophilus aphrophilus* bacteremia, brain abscess and meningitis have been associated with dental procedures on only one occasion each. Lung abscess due to *Haemophilus aphrophilus* is recorded once in the literature.

With respect to its virulence, Bieger et al. have noted a

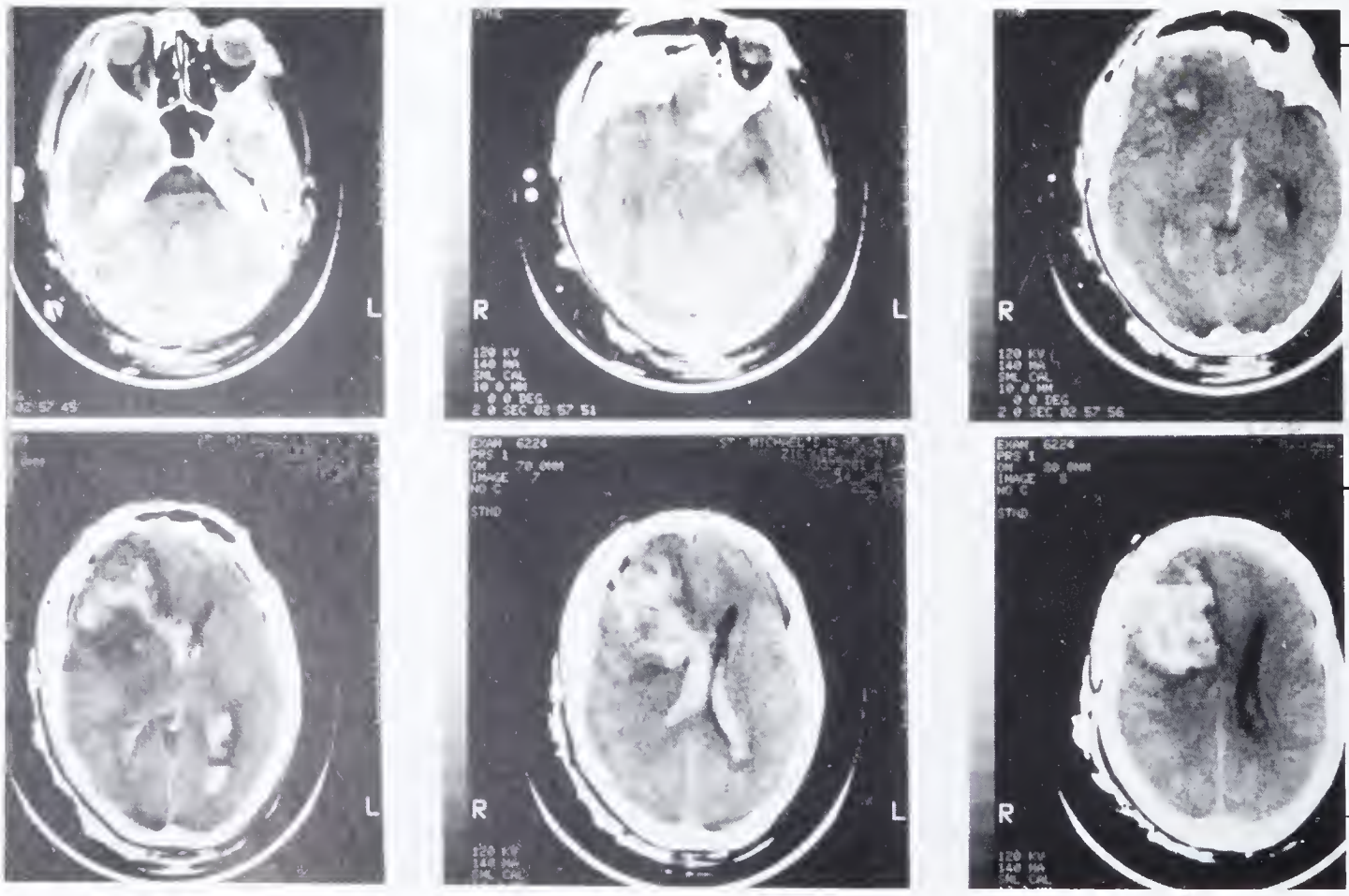


Figure 4: Case 3 – Cranial CT scan with contrast agent demonstrates right frontal lobe hemorrhage with midline shift and intraventricular extension.

high incidence of associated trauma, oral trauma and malignancy or cancer chemotherapy. This led to the conclusion that *Haemophilus aphrophilus* appears to be an "opportunist" causing disease only in the presence of a predisposing condition or tissue damage. However, in this patient there was a decided lack of associated predisposing pathology: the evidence of granulomatous disease is limited as is the extent of alcoholic liver disease.

Although its source is still disputed, *Haemophilus aphrophilus* is generally a nonpathogenic human commensal which may be isolated in approximately one-third of adults from gingival scrapings and interdental material.[5,6,7] After examining 4 247 respiratory specimens (including oropharynx, nasopharynx, sputa, bronchial washings and pleural fluid), *Haemophilus aphrophilus* was cultured in only 1.5%, suggesting that this organism is not easily surrendered to the "oral soup". Canine transmission has also been suggested, but may prove just as infectious a source as humans.[3,8,9]

The source of *Haemophilus aphrophilus* seems to be extremely specific and protected, offering high yield only by aggressive oral cultivation. It stands to reason that it generally does not provide a significant enough inoculant for infection. In this regard, a canine source might provide a greater inoculant.

Case 2: Nocardiosis

Nocardia infection itself is a rare occurrence with only an estimated 500-1000 cases per annum in the United States.[10] Central nervous system involvement by *Nocardia* is even more unusual, although approximately 15% of nocardial lung disease is associated with central nervous system involvement.[11,12,13] The majority of hosts, an estimated 85%, are immunocompromised or have some predisposing condition.[11,14] However, no history of immunosuppression was noted in this patient other than the history of alcohol abuse.

Another curious aspect to this presentation was the temporal profile of symptoms; it resulted in a clinical diagnosis of bacteremia leading to meningitis and brain abscess. Both the lack of respiratory findings in the initial presentation and the demonstration of septic emboli in the lung at autopsy, suggest that pulmonary disease was a consequence, rather than a cause, of dissemination.

Although not likely the primary site of symptomatic infection, the lung could yet have been the portal of entry and the patient's occupation might have contributed to his susceptibility. A local area of immune deficiency, either specific or nonspecific, may have been created within the lung and thereby provided the portal of entry. At the same time, this microenvironment can be inhibitory to proliferation if nutrient deficient. Hence, the first available nidus for infection becomes a question of chance reflecting hemodynamics and distribution of flow of hematogenous spread is assumed. Since the patient's illness began with symptoms of back pain which were refractive to analgesics, it may indicate that the osteomyelitis was the primary symptomatic infection.

Table I

Case	Age	Sex	History	Symptoms & Signs	Operation	Diagnosis	Treatment
1	59	M	railroad conductor, alcohol hypertension depression	drowsiness ataxia vomiting spastic paraparesis	right frontal burr hole for biopsy & ventriculostomy	*H. aphrophilus* brain abscess	Penicillin G
2	43	M	car painter, alcohol hypertension smoking	lower back pain drowsiness meningismus inappropriateness confusion obtundation	left occipital craniotomy with I&D of cerebellar abscess & ventricular drain	Nocardiosis	Septra & Penicillin G
3	53	F	rheumatic heart disease	back & leg pain fever cardiac murmur hypotension oliguria	right frontal craniotomy	CDC group M6 endocarditis with right frontal lobe hemorrhage	broad spectrum antibiotics, fluid & ICP management

I&D – Incision & Drainage
ICP – Intracranial Pressure

The ultimate demise of the patient was either due to rupture of a cerebral mycotic aneurysm or an embolic stroke with post-infarction/reperfusion hemorrhage; both mechanisms evidenced by similar pathology in the spleen.

Case 3: CDC Group M6 endocarditis

The initial report of infection caused by M6 organisms was in 1983 in a case of endocarditis. The patient responded to ampicillin, but valve replacement was eventually required.[15] These bacteria resemble certain *Moraxella* species which themselves have been rarely recognized as human pathogens. Between 1953 and 1980, the Centre for Disease Control recorded 47 isolates of M6 including 9 from sputum and 14 from the upper respiratory tract.[15] Other sources included blood, eyes, urine, wounds and peritoneal fluid. One isolate was from a fatal case of endocarditis.

In part, the rarity of infection by *Moraxella* and *Moraxella*-like species is attributable to misidentification.[15] Furthermore, group M6 organisms are apparently sensitive to commonly prescribed antibiotics (ampicillin, penicillin), which might suggest the eradication of the organisms before isolation.

In as many weeks, three rare cases of opportunistic infection with central nervous system complications presented to autopsy (Table I). Due to the precipitous course of each patient's disease, a thorough immunological evaluation was impossible. Nevertheless, not one of these young middle-aged patients offered a history which would suggest immunocompromise, and each patient tested negative for the human immunodeficiency virus (HIV). At any rate, the immunological defect in AIDS patients does not appear to predispose to bacterial infections of the central nervous system.[16,17]

When considering the epidemiology of any infectious disease, the triad of agent, host, and environmental factors must be examined with a sufficient data base. Agent factors include the duration and amount of excretion of the organism from the host, which encompasses not only cases of clinically overt disease, but also subclinical infection, incubation and carrier states, and latent infection. Also lacking from the literature is information regarding the resistance of these opportunist organisms to adverse physical conditions and their ability to establish a reservoir. Their innate pathogenicity and virulence is assumed to be low, but the possibility of mutation and even viral-mediated alteration of the DNA can still be considered. Otherwise, these opportunistic pathogens are commensal or non-pathogenic microbes which produce disease in debilitated or damaged tissues where defence mechanisms have been compromised.

Host factors similarly echo a range of potential mechanisms for increased susceptibility. Specific genetic lesions or alleles could explain immunocompromise or inappropriate immune tolerance. Also age, sex and different physiologic states are known to predispose hosts to different infectious agents and result in a variety of disease courses. The mild degree of liver disease noted in the above cases of *Haemophilus aphrophilus* and *Nocardia* infection are unlikely to be associated with detectable changes in the immune status of the hosts. Nevertheless, occasional disruptions of mechanical barriers and perturbations of metabolism likely influence the integrity of the host's defence mechanisms. The immune profile of the host may be altered by intercurrent or pre-existing diseases, neither of which were found in these cases.

Also, susceptibility to infection often reflects prior immunologic experience with the agent. Hence, the more limited the agent's reservoir, so too will be the host's immunologic experience. Lastly, human behaviour plays a significant role in increasing pathogenicity through personal hygiene, nutrition, exposure to reservoirs of the infectious agents and even in the establishment of reservoirs.

In that sense, environmental factors may be either natu-

ral or artificial. Factors such as climate, population density, food sources and vectors are also considered. These are particularly important considerations in the case of Nocardiosis where the agent is known to be a soil-dwelling saprophyte, leading to consequently greater exposure in rural areas.

The overall low incidence of infectious disease due to *Haemophilus aphrophilus* or the *Moraxella*-like species may be attributed to the difficulties in their isolation and identification. Furthermore, group M6 organisms and *Haemophilus aphrophilus* show high sensitivity to commonly prescribed antibiotics (especially ampicillin) which suggests the possibility of eradication of the organisms before their isolation.[2,15]

The occurrence of these opportunistic infections in apparently healthy hosts is especially infrequent. While this impedes an epidemiological survey, it also likely reflects the similarly rare combination of predisposing factors which must be present for infection and the development of disease.

Acknowledgement

With sincere appreciation, we thank Dr. Juan Bilbao, Department of Pathology, St. Michael's Hospital, for the use of his cases.

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Endocrine Hypertension

Ronnie Aronson 9T0, and Jay D.H. Silverberg M.D. F.R.C.P.(C) F.A.C.S.

Presentation of Case

A 38 year old man was admitted to the hospital for investigation of hypertension refractory to antihypertensive medication. He had first presented three months previously with complaints of severe, bifrontal, throbbing headaches associated with mild nausea. These headaches had progressed in frequency to the rate of one per week. The patient was found to have a diastolic blood pressure of 130 mm Hg and a serum potassium of 2.9 mmol/L. He was not on any medications at the time. He was initially treated with hydrochlorothiazide, a potassium supplement, and a ß-adrenergic blocker. After two months, his blood pressure was 210/115 mm Hg and a repeat serum potassium level was 3.3 mmol/L. The plasma renin level, measured after three hours in the upright position, was 0.03 ng/L/s (normal: 0.34–1.26). Thyroid function tests, electrocardiogram, chest radiograph and intravenous pyelogram were all negative. All hypertensive medication was stopped and the patient was admitted to hospital for further investigation.

The patient was employed as an electrician-foreman. He was a non-smoker, drank only an occasional glass of wine and had no known allergies. His past medical history included grand mal seizures over a five year period during his adolescence. He was treated with phenytoin until the age of 25, and has since been seizure-free. Family history revealed hypertension in a paternal aunt, uncle and grandfather.

On functional inquiry, the patient reported occasional palpitations and vague chest pain. His weight and energy were stable. He had not experienced flushing or excessive sweating. On examination, the patient was an obese man who appeared well. The blood pressure in the right arm was 160/100 mm Hg supine, 135/100 mm Hg upright and the heart rate was 76 beats/minute. Examination of the head and neck was unremarkable except for arteriolar narrowing and A-V nicking in the fundi. Visual fields were full. The chest was clear, the heart sounds were normal and regular, and peripheral pulses were palpable with no audible bruits. Abdominal examination was unremarkable; no mass was palpated. The deep tendon reflexes were normal, and distal sensation was intact.

The urine was negative for protein, glucose and ketones. However, the sediment was found to contain a few leukocytes and erythrocytes on high-power examination. Serum electrolytes were as follows: sodium 145 mmol/L, potassium 3.5 mmol/L, chloride 105 mmol/L, and bicarbonate 31 mmol/L. The blood urea nitrogen was 8 mmol/L and the serum creatinine 110 umol/L. In a 24-hour urine specimen of 900 ml, the sodium was 110 (50–150) mmol, the potassium 70 (20–120) mmol, the creatinine 14.7 (7.0–16.0) mmol, the free cortisol 177 (28–280) mmol, the vanillylmandelic acid (VMA) 31 (9–36) mmol, and the 17-ketosteroids 64 (20–70) mmol.

The electrocardiogram was within normal limits. An abdominal ultrasound examination was normal, but an abdominal CT scan revealed a 1.5 cm spherical mass at the superior pole of the left adrenal gland.

While in hospital, the patient's blood pressure ranged between 140/95 and 170/110 mm Hg. His potassium ranged from 3.2 to 3.6 mmol/L and he remained asymptomatic.

A series of investigations were performed.

Differential Diagnosis

This 38 year old man presented to the referring physician with headaches and was found to be hypertensive and hyponatremic. Treatment with diuretics and ß-blockers had not improved his hypertension. Physical examination, other than retinal changes, was unremarkable. A CT scan of the abdomen revealed a left adrenal mass.

In patients with **1** arterial hypertension, **2** hypokalemia with inappropriately elevated urinary potassium excretion, and **3** suppressed plasma renin, the diagnosis of primary aldosteronism (PA) should be considered. Though PA accounts for only 0.5%–2.0% of hypertension in the general population, this proportion may be much higher at tertiary care centres.[1] In fact, in hypertensive patients with unexplained hypokalemia, PA is the cause in 50%.[1] This prevalence may be further underestimated, according to reports suggesting that serum potassium and plasma renin concentrations are unreliable as screening techniques. One study has demonstrated normokalemia in 27% of proven PA and normal to high plasma renin concentrations in 28%.[2]

The commonest cause of PA is adrenal adenoma (65%), with another 34% due to idiopathic bilateral adrenal hyperplasia.[1] Adrenal hyperplasia may be further subdivided into idiopathic hyperaldosteronism and dexamethasone-suppressible aldosteronism which is an ACTH-dependent, autosomal dominant condition.[3] Recently, elevated levels of a glycoprotein, aldosterone-stimulating factor, have been associated with idiopathic hyperplasia,[4] but a causal relationship has not yet been established. Adrenal carcinoma accounts for less than 1% of patients with PA.[1]

Aldosterone is a steroid hormone secreted by the zona glomerulosa of the adrenal cortex. It acts at the distal convoluted tubule (DCT) of the nephron to stimulate sodium reabsorption and cause diffusion of potassium and

secretion of hydrogen into the lumen. Aldosterone secretion is regulated by three separate mechanisms. The most important mechanism is the renin-angiotensin system acting via angiotensin II. It reacts primarily in response to decreased effective circulating plasma volume (ECPV). Aldosterone secretion by the zona glomerulosa is also very sensitive to changes in serum potassium concentrations, varying directly with the potassium level. ACTH, as the third regulatory factor, can produce an acute increase in aldosterone secretion. Dopamine, serotonin and atrial natriuretic factor may also have some role in the regulation of aldosterone secretion.

The clinical features of PA are all explained by the effects of aldosterone at the renal DCT. Increased mineralocorticoid activity causes expansion of the extracellular volume by up to two litres. This volume expansion is limited by the "mineralocorticoid escape" phenomenon: sodium reabsorption at the proximal convoluted tubule is reduced, thus counteracting the increased DCT reabsorption. Down-regulation of the DCT receptors for mineralocorticoid may also account for stabilization.[5] The increased excretion of potassium and hydrogen ions causes hypokalemia with increased or inappropriately normal urinary potassium excretion and a mild metabolic alkalosis. The hypervolemia suppresses renal production of renin, producing the characteristic low plasma renin concentrations.

The presentation usually involves hypertension, diagnosed incidentally or because of the sequelae of coronary, aortic, renal, and cerebral atherosclerosis. Hypokalemia occurs spontaneously in 80-90% of patients with PA and may be easily induced in the remainder by ingestion of a high sodium diet (100 mg/day) over three to five days.[1] Signs and symptoms may include myopathy and paresthesia, polyuria, hyposthenuria, polydypsia and impaired glucose tolerance (due to impaired insulin release) (Table I).[6] In PA, serum potassium concentrations do not fall indefinitely because of feedback regulation. Severe hypokalemia prevents continued aldosterone secretion, allowing a return to normokalemia.

In a hypertensive patient, the most common cause of hypokalemia is previous diuretic use. To rule this out, diuretic therapy must be stopped for three days before serum and urinary potassium levels are checked.[7] The possibility of gastrointestinal losses due to laxative abuse, chronic diarrhea, or vomiting should be considered. Renal tubular acidosis and carbenicillin use can also cause hypokalemia. In taking blood, tourniquet use, arm exercise and venous stasis should be avoided, as they may increase serum potassium.

In assessing the plasma renin level, blood should be drawn after performance of a procedure to decrease ECPV, such as standing upright or giving diuretics.

Mineralocorticoid excess may also be due to secondary, extra-adrenal stimuli, such as exaggerated renin-angiotensin activity, glucocorticoid excess, congenital adrenal hyperplasia or ingestion of materials with hormone activity (Table II). These causes are usually easily excluded.

In malignant hypertension, prolonged renal microvascular injury causes elevated serum aldosterone concentrations and hypokalemia, closely resembling PA. However, malignant hypertension can be excluded because of its severity and accompanying retinal hemorrhages, papilledema, and elevated plasma renin level. PA is rarely associated with severe hypertension.[2]

Table I

CLINICAL CHARACTERISTICS OF PRIMARY ALDOSTERONISM

Muscle weakness	73%
Polyuria	72%
Headache	51%
Paresthesia	24%
Intermittent paralysis	21%
Tetany	21%

Hypertension may be due to renovascular disease or to renin-secreting neoplasms such as benign juxtaglomerular cell tumours, Wilm's tumour, and renal, pulmonary or pancreatic adenocarcinoma. Although each of these disorders involves elevated aldosterone concentrations with hypokalemia, they can be distinguished from PA by their elevated plasma renin levels.

The presence of an adrenal mass identified in this patient requires evaluation of the remaining adrenal causes of hypertension. Glucocorticoid excess may present as hypertension with hypokalemia and relatively few clinical features of Cushing's syndrome. In ectopic ACTH production and in glucocorticoid-secreting neoplasms, deoxycorticosterone (DOC), a mineralocorticoid precursor, is synthesized. With augmentation by the mineralocorticoid properties of cortisol, hypertension with hypokalemia may result. In the hypertensive patient, one may use either an overnight dexamethasone suppression test (morning plasma cortisol is measured after 1 mg dexamethasone administration the previous night) or a 24-hour urine free cortisol assay to rule out Cushing's syndrome. Our patient showed none of the clinical features of Cushing's syndrome, including moon facies, cervicodorsal fat deposition, glucosuria, acne, plethora or atrophic skin. He also had normal excretion of free cortisol in a 24-hour urine sample.

Refractory hypertension with hypokalemia, headache and adrenal mass also suggests the diagnosis of pheochromocytoma, a catecholamine-secreting tumor of the adrenal medulla, present in 0.5% of hypertensive patients.[8] Pheochromocytoma classically presents with hypertension and the clinical triad of tachycardia, headaches and excessive sweating in a paroxysmal pattern. A Mayo clinic review of autopsy-identified pheochromocytoma[9] found that 78% had not been suspected, despite hypertension with the above clinical features. To exclude the diagnosis of pheochromocytoma, 24-hour urinary concentrations of catecholamines and their metabolites, metanephrine and VMA, may be measured. Plasma catecholamine measurements may be useful during or immediately after an acute episode. Although pheochromocytoma is associated with elevated plasma renin, it was ruled out in this patient by a normal daily excretion of VMA.

Congenital causes of excess mineralocorticoid include two forms of congenital adrenal hyperplasia (CAH): 11-ß-hydroxylase and 17-α-hydroxylase enzyme deficiencies. Impaired glucocorticoid production allows ACTH release, causing mineralocorticoid (DOC) overproduction. In the 17-hydroxylase form, all further steroid pathways are blocked, but in 11-hydroxylase deficiency androgen production continues with virilization or precocious puberty. Both disorders may present in the adult and represent rare, though correctable, forms of endocrine hypertension. Liddle's syndrome is a familial, congenital disorder which causes hypertension with hypokalemic alkalosis and normal mineralocorticoid levels.[10]

Two iatrogenic causes of secondary hyperaldosteronism have been reported, including ingestion of licorice, which contains the mineralocorticoid glycyrrhizin,[11] and use of the nasal spray biorinal, which contains 9-α-fluoroprednisolone.[12] Oral contraceptives can cause renin-aldosterone hyperactivity with hypertension. The distinguishing feature in oral contraceptive use is an elevated renin level.[13]

Diagnosis

The definitive diagnosis of PA requires investigations which show evidence of simultaneous **1** elevated plasma or urinary aldosterone concentrations with no significant decrease after an acute suppresion test involving infusion of two litres of normal saline;[14] and **2** decreased plasma renin concentration with no increase after stimulatory test involving furosemide or prolonged standing.

Although captopril, which can depress aldosterone production, has been used in suppression testing, a recent Japanese study[15] found higher specificity using the serum renin and aldosterone concentrations expressed as a ratio. Some reports have improved specificity with a portable intravenous catheter pump to sample aldosterone over a longer period and thus avoid random fluctuations.

Once a diagnosis of PA has been made, the etiology of the disorder has important therapeutic implications. Surgical intervention is usually curative for aldosterone-producing adenoma (APA) and is rarely effective for idiopathic hyperaldosteronism (IHA). Clinical differentiation between APA and IHA is poor. APA is associated with higher blood pressure and plasma aldosterone values, and lower serum potassium and plasma renin values, relative to IHA figures. However, the ranges of each of these variables in APA and in IHA overlap considerably. Bravo et al. found a distinguishing feature of APA: an anomalous decrease in plasma aldosterone with upright posture.[2] This decrease was present in half of the patients with APA but did not appear in the IHA patients. Several studies[17,18] have measured the mineralocorticoid 18-hydroxy-corticosterone as a baseline or after an infusion of saline. Elevated levels after this suppressive test reliably diagnosed autonomous production (APA). To rule out the presence of an ACTH-dependent tumour, a dexamethasone suppression test may be used.

In patients with an aldosterone-producing tumour, preoperative localization of the tumour simplifies the surgical procedure and significantly reduces morbidity. Various techniques are listed in Table III. Adrenal scanning, using radioactive iodine-labelled cholesterol and dexamethasone-induced suppression of the remainder of the gland, shows poor sensitivity in various studies, ranging from 46%–88%.[13,21-23] Another non-invasive test, the CT scan, was slightly more sensitive, ranging from 70%–90%.[19-23] The most effective tumour localizing tool, however, is bilateral adrenal vein sampling, with sensitivity usually above 90% in experienced hands.[13,20] Therefore, if biochemical evidence suggests APA, a CT scan should be performed and considered diagnostic if an adrenal mass is identified. Adrenal venous sampling should be used if the results of the CT are inconclusive.

Spironolactone, an aldosterone receptor blocker, is also useful as a predictor of surgical response. Saruta et al.[24] showed that 97% of responders to spironolactone (mean blood pressure fall > 15 mm Hg) became normotensive (< 160/95 mm Hg) after unilateral adrenalectomy. Of the non-responders to spironolactone, none became normotensive after surgery.

The definitive diagnosis in this patient was made using a series of biochemical investigations. The initial concentration of aldosterone was 900 pmol/L (normal: 140–420 pmol/L). The plasma renin level was 0.12 ng/L/s (normal: 0.18–0.74 ng/L/s). Renin levels remained suppressed despite the stimulatory tests of standing upright for two hours (0.09 ng/L/s) and post-infusion of furosemide (0.10 ng/L/s). Aldosterone concentrations did not decrease after infusion of two litres of normal saline, but did show an anomalous decrease after two hours of standing (1210 to 860 pmol/L), indicating APA.

Also consistent with PA, a captopril suppression test resulted in no change in either aldosterone concentration or renin concentrations. Interestingly, after administration of dexamethasone the aldosterone level did fall, but did not meet the criteria for glucocorticoid-suppressible PA.

To confirm the CT finding of a left adrenal mass, an adrenal scan was performed using radioactive iodine-labelled cholesterol, with the remainder of the gland suppressed by dexamethasone. The scan showed an area of uptake in the left adrenal gland consistent with adrenal adenoma.

Table III

SENSITIVITY OF PREOPERATIVE TUMOUR LOCALIZATION TOOLS

Adrenal Scan	*CT*	*Venous Sampling*	*Author*
46%	—	100%	Weinberger et al, 1979
—	88%	76%	McAreavy et al, 1981
—	70%	96%	Geisinger et al, 1983
88%	88%	—	Grant et al, 1984
69%	80%	—	Vetter et al, 1985
50%	90%	—	Lim et al, 1986

Over this interval, the patient was maintained on spironolactone. He responded with a 25 mm Hg decrease in mean blood pressure, a good prognostic sign for post-adrenalectomy response.

Table II

DIFFERENTIAL DIAGNOSIS OF PRIMARY ALDOSTERONISM

	Plasma Renin	*Plasma Aldosterone*	*Blood Pressure*	*Serum Potassium*
Primary Aldosteronism	low	high	high	low
Malignant hypertension	high	high	high	low
Renovascular hypertension	normal/high	normal/high	high	normal/low
Renin-secreting tumours	high	high	high	normal/low
Cushing's syndrome	low/normal	normal/low	high	low
CAH	low	low	high	low
Liddle's syndrome	low	low	high	low
Licorice ingestion	low	low	high	low
Nasal spray (Biorinal)	low	low	high	low
Oral contranceptives	high	high	high	normal

Treatment

The treatment of choice for adrenal adenoma is unilateral adrenalectomy. Various follow-up studies report improvements in blood pressure in 95%–100% of patients, and complete normalization in 60%.[25-26] In IHA the antihypertensive, potassium-sparing diuretics such as spironolactone and amiloride should form the first-line medication. These may be supplemented by nifedipine, a calcium-channel blocker shown to be effective in PA management,[27] angiotensin-converting-enzyme inhibitors, and adrenergic blockers as required. Ketoconazole, a mineralocorticoid synthesis blocker, has also been found to be effective in pre-operative blood pressure management in PA.

The patient was admitted to hospital for left adrenalectomy three months after his initial presentation. Pathology revealed a 1.2 cm and a 0.3 cm cortical mass. Both showed architecture consistent with glomerular and fasciculate zones and were diagnosed as adrenal cortical adenomas. The patient's hypertension resolved immediately post-adrenalectomy and he has remained normotensive at follow up four years later.

Summary

In a patient with hypertension, hypokalemia (while off diuretics) and suppressed plasma renin levels, the diagnosis of primary aldosteronism should be considered. These parameters are unreliable for general screening of the hypertensive population. Plasma or urinary aldosterone concentrations, after a suppressive test of saline infusion, must be determined. The same saline infusion also clarifies the etiology, as elevated mineralocorticoid levels suggest adenomatous disease. Severe hypokalemia and a decrease in plasma aldosterone with upright posture also indicate an aldosterone-producing adenoma. In APA, pre-operative localization should be performed initially using CT scan and progressing to adrenal venous sampling if necessary.

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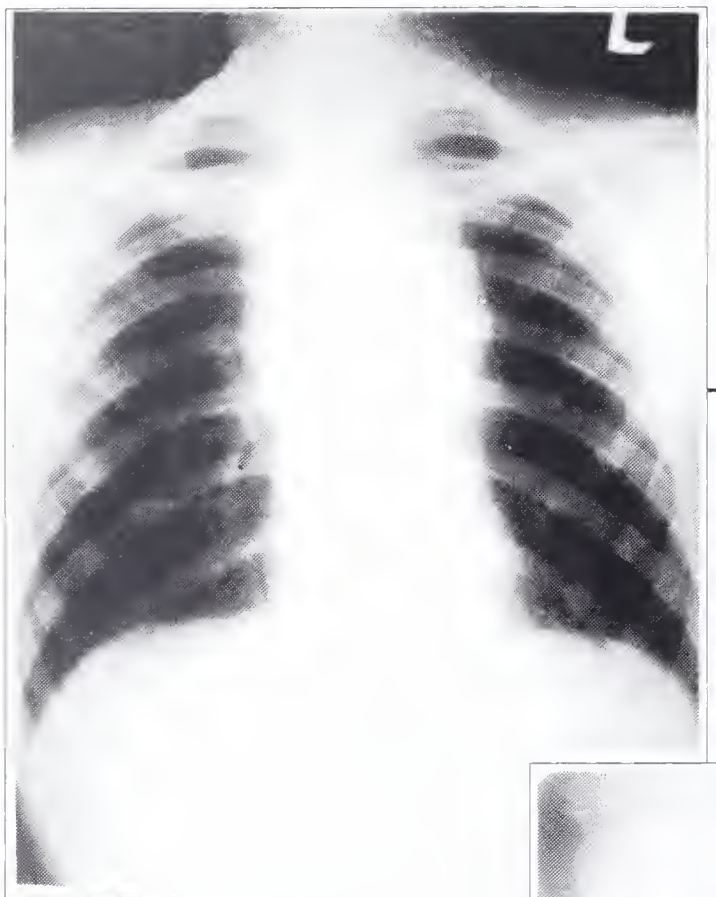
X-Ray Use in Cardiology and Respirology

Arif Naqvi 9T1

Give a provisional diagnosis for each of the following cases:

Case 1

An 18 year old male presented with cough, fatigue, chest discomfort and extreme shortness of breath. Physical examination revealed enlarged supraclavicular and cervical nodes.

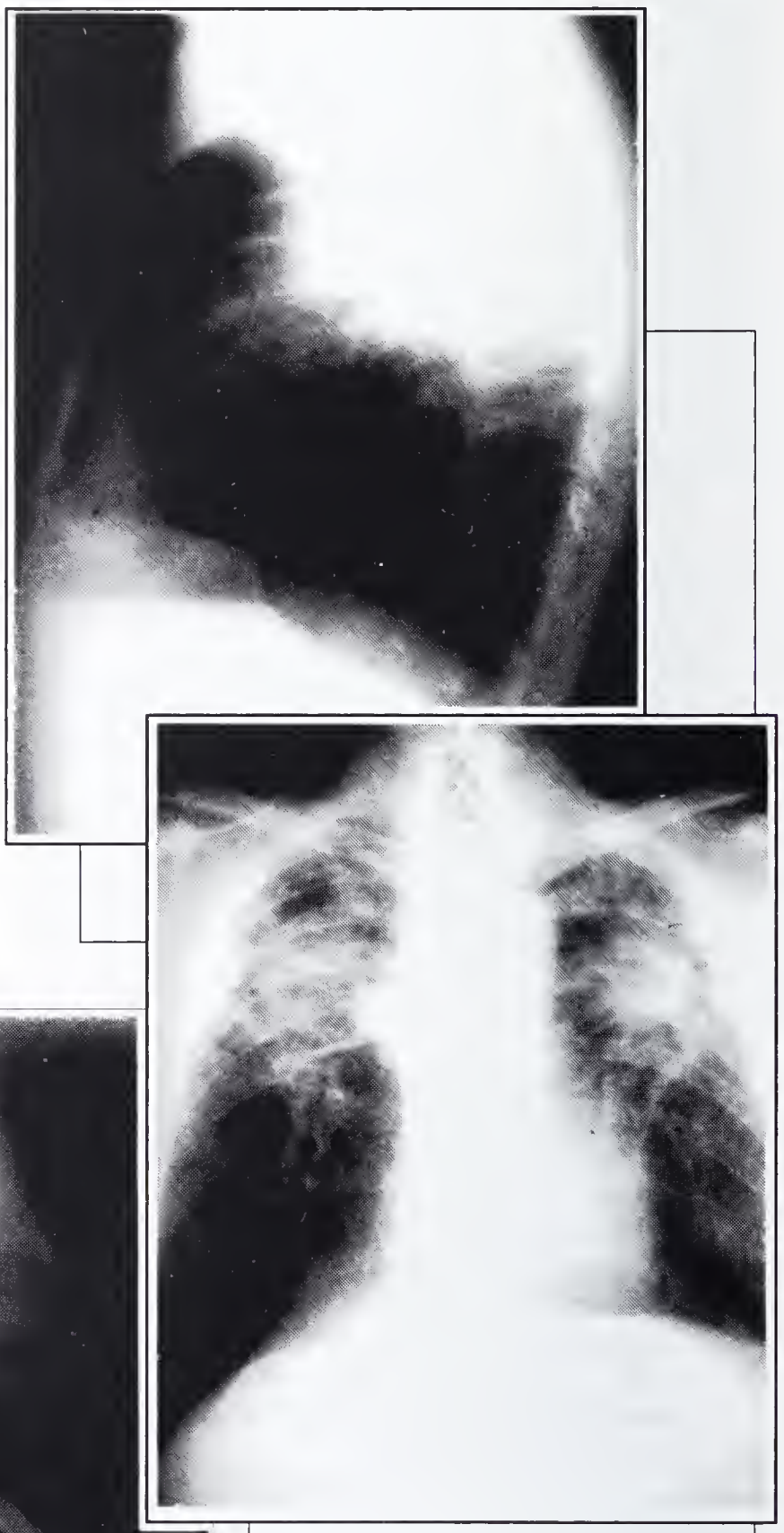


Answer Case 1

The anterior mediastinum shows an opacification in the lateral projection. There is also widespread involvement of the tracheobronchial and hilar lymph nodes bilaterally. This is the classic presentation of Hodgkin's disease.

The infiltrating tumour later spread into the mediastinum and the adjacent lung parenchyma. The esophagus and the stomach were soon obstructed by metastatic disease and eventually it spread to all extrathoracic nodes.

The patient died five months after this x-ray was taken.



Case 2

This 61 year old male presented with shortness of breath on exertion. He has worked in gold mines for most of his life. Physical examination was normal.

Answer Case 2

This patient has severe, complicated silicosis. This disease is commonly found in workers involved in gold, tin, copper and mica mining industries. The toxic material in silicosis is silicon dioxide. Exposure to silicon dioxide also occurs in such industries as quarrying and tunneling and rare cases have been described in persons with excessive exposure to ajax, the cleaning powder.

The fine nodular shadows are the result of small silicotic nodules in the peribronchiolar lymphatic tissue and parenchyma. These have conglomerated to form massive nodules indicating accelerated progression of the disease.

Case 3

This 26 year old female presented to the hospital complaining of exertional dyspnea, dizziness, and occasional cyanosis of her lips. She was born a "blue baby".

Answer Case 3

She was born with Tetralogy of Fallot. The cardiac apex is elevated from the left hemidiaphragm, a finding typical of Tetralogy of Fallot. The pulmonary arterial supply to the right lung and lower half of the left lung appears slightly decreased. The vessels in the upper half of the left lobe are the bronchial arteries which are characteristically enlarged.

The rib notching on the undersurfaces of the upper ribs is due to bilateral Blalock shunts.

Case 4

On admission, Miss W.R., 45, was mildly orthopneic with nontender hepatomegaly, probable ascites and pitting edema.

A grade III ejection systolic murmur was heard at the left sternal border and a loud early diastolic rumble heard at the apex. A faint opening snap was present.

Miss W.R. had rheumatic fever and Sydenham's Chorea at the age of 7 and was unable to keep up with her peers. A heart murmur was first noted at age 12. At age 37, she underwent mitral valve split to relieve the symptoms of shortness of breath and swelling of the ankles. She was well again until the age of 43 when she developed swelling of the ankles, shortness of breath, ascites and occasional angina. She has been in and out of heart failure several times. At present, she is able to walk a 1/2 block on the level.

Answer Case 4

Miss W.R. has Lutembacher's syndrome. She was born with an atrial septal defect (ASD) and acquired mitral valve stenosis secondary to rheumatic fever.

Note the gross cardiac enlargement with an extremely high cardio-thoracic ratio. Note also the large pulmonary outflow tract and the small aortic knob. Both atria and the right ventricle are enlarged. Pulmonary plethora indicates a left to right shunt.

These findings are suggestive of combined mitral valve stenosis and an ASD which together constitute the Lutembacher syndrome.

Vellore Town: It's chaos outside but the hospital looms white and pristine in the distance.

We Will Put Them in Our Hearts

Jay D. Raisen 9T0 and *Alice A. Newmann 9T0*

We would like to dedicate this article to S. Ayyappan, a dear friend who died unexpectedly on January 5, 1989, in Nagpur, India, waiting for an ambulance.

We went to Southern India in the summer between our second and third year of medical school to study at the Christian Medical College in Vellore. The journey there involved a three hour hair-raising bus trip along the one and a half lane Madras-Bangalore highway, with three hundred other people, some hanging out of the doors.

A private institution, CMC operates a variety of medical education, research and development programs as well as a number of medical care facilities which include a general hospital that is widely held to be one of India's finest. CMC's staff, student and patient population come from all over India and surrounding countries, forming a small cosmopolitan subculture in a predominantly rural area. Although CMC can be compared to the University of Toronto in scope, the two schools' ethos and approaches are derived from distinctly different realities. There is, for example, the huge population to contend with. The main hospital cares for approximately 1000 outpatients and 1000 inpatients each day. These figures alone are impressive, but they give poor estimate as to the true numbers filling the wards, corridors and courtyards of the hospital complex. Every Indian patient comes with a large extended family translating into a veritable tide of people eating, sleeping and waiting on line, or simply milling about. In spite of all this traffic, the hospital is immaculately clean and smells strongly of carbolic acid disinfectant. Hundreds of overhead fans and large screenless windows moderate the forty degree heat. It is a haven from the intense sun, choking dust, and considerable confusion of the bazaar-lined streets outside.

The mada lady whom we met on the coconut balm lined western seacoast. She sports one tooth.

Most of our time was spent with the department called CHAD (Community Health and Development). CHAD operates a small 100 bed primary health centre and mobile clinics which ensure biweekly visits to the approximately 100 villages in Vellore's environs. CHAD has attempted to intertwine modern medical care into the intricate fibre of village India by setting up a health care pyramid which employs well respected village members such as midwives or traditional Ayurvedic practitioners as frontline care givers. CHAD trains these people as part time health workers, instructing them in basic first aid, sanitation, oral rehydration, and nutrition, etc. CHAD organizes a multitude of community programs which focus on socioeconomic development in keeping with an expanded notion of health care.

We became uncomfortably aware of what it meant to work in a resource limited health care system. Laparotomies for tubal ligations are carried out by interns, unassisted, using xylocaine, valium and cotton sutures. In this type of system, the good of the community is a higher priority than that of the individual. Therefore, tremendous energy is devoted to evaluate the efficacy of existing programs in order to ensure that they address the community's needs.

Our experience with CHAD and, in particular, an exceptional young doctor who befriended us, lent insight into matters of which we previously had no understanding. He showed us the villager's way of life, their poverty, their lack of opportunity, their lack of education, and their strong traditions. He attempted to instill respect for the village culture to demonstrate how a community's ways must be incorporated into any successful health care strategy, particularly in a developing country.

Our milk bar – after a startling introduction to the place, we grew to like it and came in the afternoon for a glass of hot sweet milk.

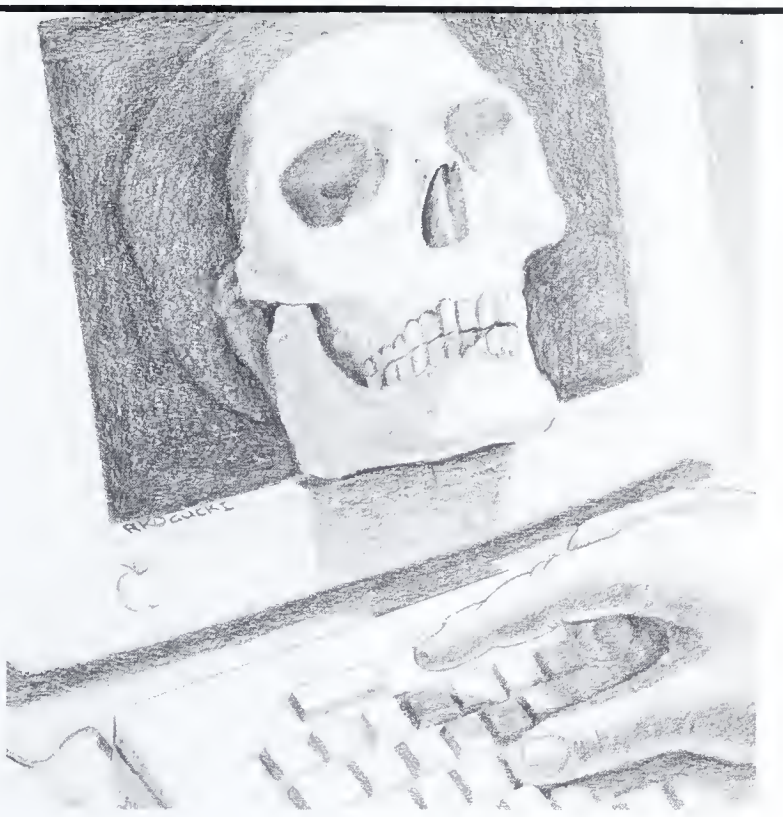
The hill people and our CMC van.

Several points were quite striking in Vellore: one encounters types and advanced presentations of disease which in Canada are endemic only in medical texts; clinicians rely almost exclusively on their sound clinical skills for diagnosis; alcoholism, not malaria, is endemic in the district; motor vehicle accidents produce more mortality than infectious disease (especially to foreign health care workers); and there is little severe malnutrition, only hundreds and hundreds of beautiful smiling children, many of whom work in Vellore's shops.

There is no way to neatly summarize our experience in India. It would suffice to say that we arrived as uninitiated Canadians, went through painful adjustment phases, and then adapted and learned a great deal. We came back with friends we will never forget and ideas that will probably alter the course of our lives.

One day we stopped at a roadside village on our way to a clinic far in the hills. The CMC van in which we were travelling was full but the physician in charge offered a lift to two government health care workers.

"Where will we put them?" He smiled and said serenely, "We will put them in our hearts."



MEDLINE on CD ROM

Mohammed Nizar Mahomed 9T2

For most medical professionals who wished to find journal articles related to a given topic, it meant a trip to the nearest medical library in order to leaf through the numerous volumes of the Index Medicus. A few years ago, the National Library of Medicine in Bethesda, Maryland began transferring the Index Medicus onto computer and then selling copies of the computerized Index as MEDLINE to various private and non-private vendors.

Initially, these vendors made available the MEDLINE information on a fee per hour basis through on line database networks. In order to access these systems, one has to sign a contract, undergo a training session, and pay user fees in the form of membership, monthly dues, hourly charges, and for the number of articles searched. This made the MEDLINE service all but inaccessible to individuals with limited resources.

With the advent of CD ROM, this system is now readily available to a wide variety of medical users. The term CD ROM is an acronym for Compact Disk Read Only Memory. Essentially a CD ROM is a Compact Disc Player with a special controller system incorporated into a single unit. This enables the use of Compact Disks as a mass data retrieval system for large databases and electronic publications. A single disk has a Read Only capacity of 650 Mega-Bytes, roughly equal to 130,000 pages of information. These units can be connected to most personal computers converting them into powerful reference tools. Various vendors have now made available the MEDLINE database in the form of compact discs sold in yearly packages.

The advantage of such a system over the various on line versions of MEDLINE is the long term cost. Although the cost of the CD may seem considerable initially, there is no further membership nor on line charges for their use. This results in substantial savings over the course of the year if one considers the cost of each individual search conducted through telecommunication networks.

The Science and Medicine Library at the University of Toronto has recently acquired a personal computer with the MEDLINE on CD system which is marketed by Cambridge Scientific Abstracts. They offer a free one hour introduction to the system at various times during the year. Once acquainted with it's usage, one may reserve a session on the system and perform the same search as one would on the network versions for no charge. This makes the advances of computerized searching, with cross indexing and other features, available to interested users free of charge.

The Sigmund Samuel Library has recently installed a similar system that contains the MEDLINE database along with a variety of journals and textbooks on CD. The library also offers a full day course on searching computerized databases and has an END-USER Service which allows students to access MEDLINE and other databases on line for a fee.

The advantages of using this system over the printed INDEX MEDICUS are obvious. The computerized system provides a quick and accurate means of searching for articles over the past few years in a matter of minutes. This results in a saving of valuable time, especially if one is searching for a sizeable number of articles. Another benefit is that the CD version provides an abstract for each article selected, in addition to a list of references, enabling one to weigh the suitability of the article to one's needs without having to search through the stacks to locate it first.

The only disadvantage is that it is available only on one computer presently and is not accessible to students via terminals across the campus. The Science and Medicine Library and the Sigmund Samuel Library hope to enhance the access to their Compact Disk databases by connecting one of the systems to the existing computer terminal network sometime in the future.

In conclusion, the MEDLINE on CD ROM makes available the power of computerized searching at a modest cost enabling individuals to harness the power of MEDLINE. For faculty and students this power is available through the Science and Medicine Library at no charge. It represents a valuable time saving tool to any researcher, clinician, or other medical professional.

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NEWS UPDATES

Important Recent Discoveries About the Functions of "Immune Response" Genes

The discovery that immune responses are controlled by gene products encoded by the Major Histocompatibility Complex (MHC) on chromosome 6 (in humans) in the late 1960's has led immunologists down a long and tortuous path. One of the landmark discoveries was made by Zinkunagel and Doherty in 1974, who observed that virus antigens are recognized and responded to by T lymphocytes in association with MHC gene products. Experiments carried out by a number of labs since that time indicate that cytotoxic and helper T lymphocytes become activated and carry out their respective functions when they recognize antigen and class I or class II MHC molecules on specialized antigen-presenting cells. The biochemical and structural requirements of the complex process of antigen presentation and T cell recognition are not known with accuracy, but recent experiments published by Townsend et al. shed further light on these events. This group studied a mutant mouse cell line, RMA-S, which expresses 5% of normal levels of class I MHC molecules on its cell surface. This cell line expresses both class 1 heavy chains and Beta-2 microglobulin, but there is a defect in the association products. The interesting observations are as follows. First, killer T cells (CTL's) can recognize and kill influenza-virus-infected RMA (the normal parent cell line), but not infected RMA-S cells. Second, if either cell line is incubated with purified, synthetic flu-virus peptides which the CTL is known to recognize, both cell lines are killed. By further experimentation Townsend and his co-workers were able to construct an interesting model. It appears that incubating RMA-S cells with peptide allows the cell surface expression of a complex of complete class I molecule plus peptide, which can then be recognized by the killer T cell. The defect in expression is not completely corrected (MHC levels go from 5% to 20% of normal levels), but it is sufficient to allow recognition by the T cell.

The biochemical process by which antigens are degraded and become associated with MHC molecules in cells like the macrophage or Langerhans cell is not understood. The results of Townsend et al. suggest that the sequence of events may be as follows. Prior to binding beta-2-m the heavy chain may interact with a peptide. Heavy chains that bind to an appropriate (compatible) peptide achieve a conformation which allows binding to beta-2-m and transport to the cell surface, where the complex can be recognized by the T cell. The caveat with these experiments, however, is that the mutation in RA-S is not known and it is possible that the cell line lacks a third molecule important in the transport of MHC molecules to the cell surface. For more information the interested reader is referred to Townsend et al. Association of Class I Major Histocompatibility Heavy and Light Chains Induced by Viral Peptides. Nature 1989; 340:443-448.

12th Annual Bristol Myers Symposium on Cancer Research

The 12th Annual Bristol-Myers Symposium on Cancer Research was held at the Four Seasons Hotel in Toronto on September 26th and 27th, 1989 and featured several well-known researchers from Toronto and other international centres as keynote speakers. Dr. Daniel Bergsagel of the Princess Margaret Hospital in Toronto inaugurated the meeting in his capacity as chairman of the Symposium Committee.

The first day of the meeting featured two sessions on the fundamental genetics and biology of cancer. The morning session, chaired by Dr. Tak Mak (Toronto), was entitled "The Genetic Basis of Neoplasia". Dr. Phillip Sharp (MIT) provided an overview of the mechanisms of the regulation of normal gene expression and the role of alterations in normal gene expression in oncogenesis. Dr. Michael Bishop (San Francisco), recent co-recipient of the 1989 Nobel Prize in Medicine and Physiology, discussed the current state of knowledge of the role of oncogenes in the development of cancer in several animal model systems. Also featured in this session were Dr. Phillip Leder (Boston), who discussed a model of oncogenesis using a mouse mammary tumour virus promoter (c-myc gene) construct in transgenic mice, and Dr. Tak Mak who discussed T cell receptor gene expression in normal and malignant T cell development.

The afternoon session, chaired by Dr. Ron Buick (Toronto) focused on the biology and genetics of three specific tumours. Dr. R.A. Phillips (Toronto) provided an overview of structural and functional mutations at the retinoblastoma locus on chromosome 13. The retinoblastoma "gene" was one of a group of so-called "recessive" oncogenes discussed that afternoon. In very simple terms, the loss or alteration of genetic material at "recessive" oncogene loci allows the expression of a neoplastic phenotype in cells in which such modifications occur. Sir Walter Bodmer (Oxford) presented results which indicate that similar mechanisms may operate in certain forms of colo-rectal cancer such as that associated with familial polyposis. Although the gene(s) involved has not been isolated RFLP analysis has localized the problem to chromosome 5q21.

Wednesday's two sessions addressed the therapeutic aspects of the cancer problem and future avenues of investigation to improve both diagnosis and treatment. In the morning session Dr. Victor Ling (Toronto) discussed the role of drug-resistance in chemotherapy, particularly the role of the 170 Kd P glycoprotein which has been implicated as an important mediator of multi-drug resistance in animal models systems and possibly in certain human tumours. In an interesting presentation Dr. Kevin Tracey discussed the role of cachectin (tumour necrosis factor) in inducing metabolic changes which lead to wasting and death in cancer, parasite infections and other chronic disease states. Tracey discussed the changes induced in ex-

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You CH, Lee K, Chey WY, Menguy R. Electogastrographic study: a patient with unexplained nausea, bloating and vomiting. Gastro-enterology 1980; 79:311-314.

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